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The Western Journal of Medicine

VOLUME 150 • NUMBER 1 JANUARY 1989

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The portrait of anxiety

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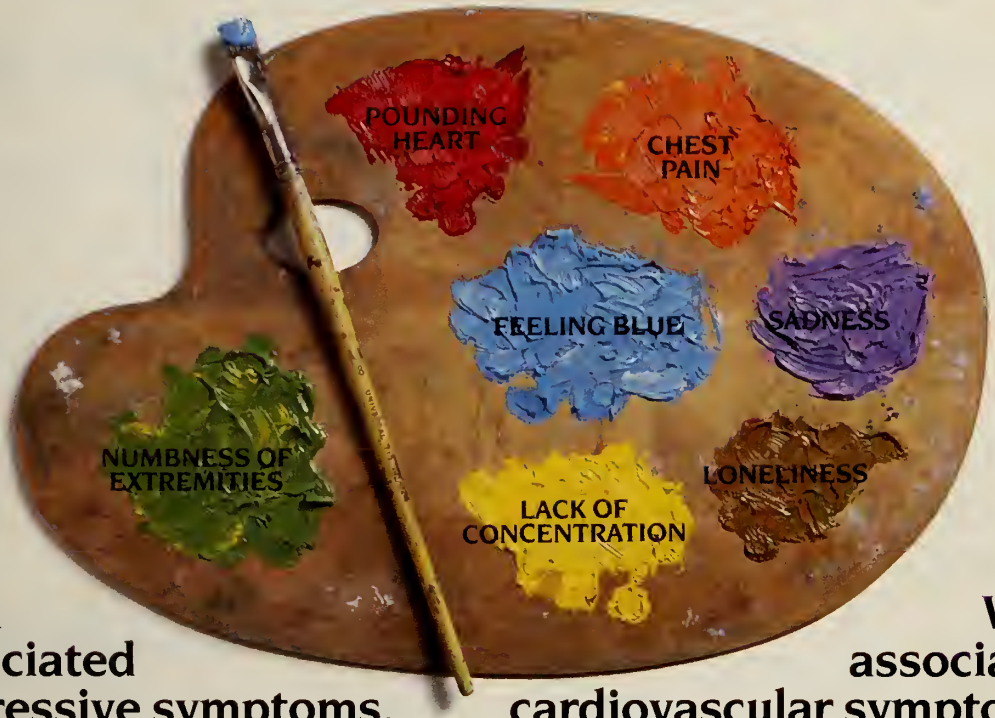
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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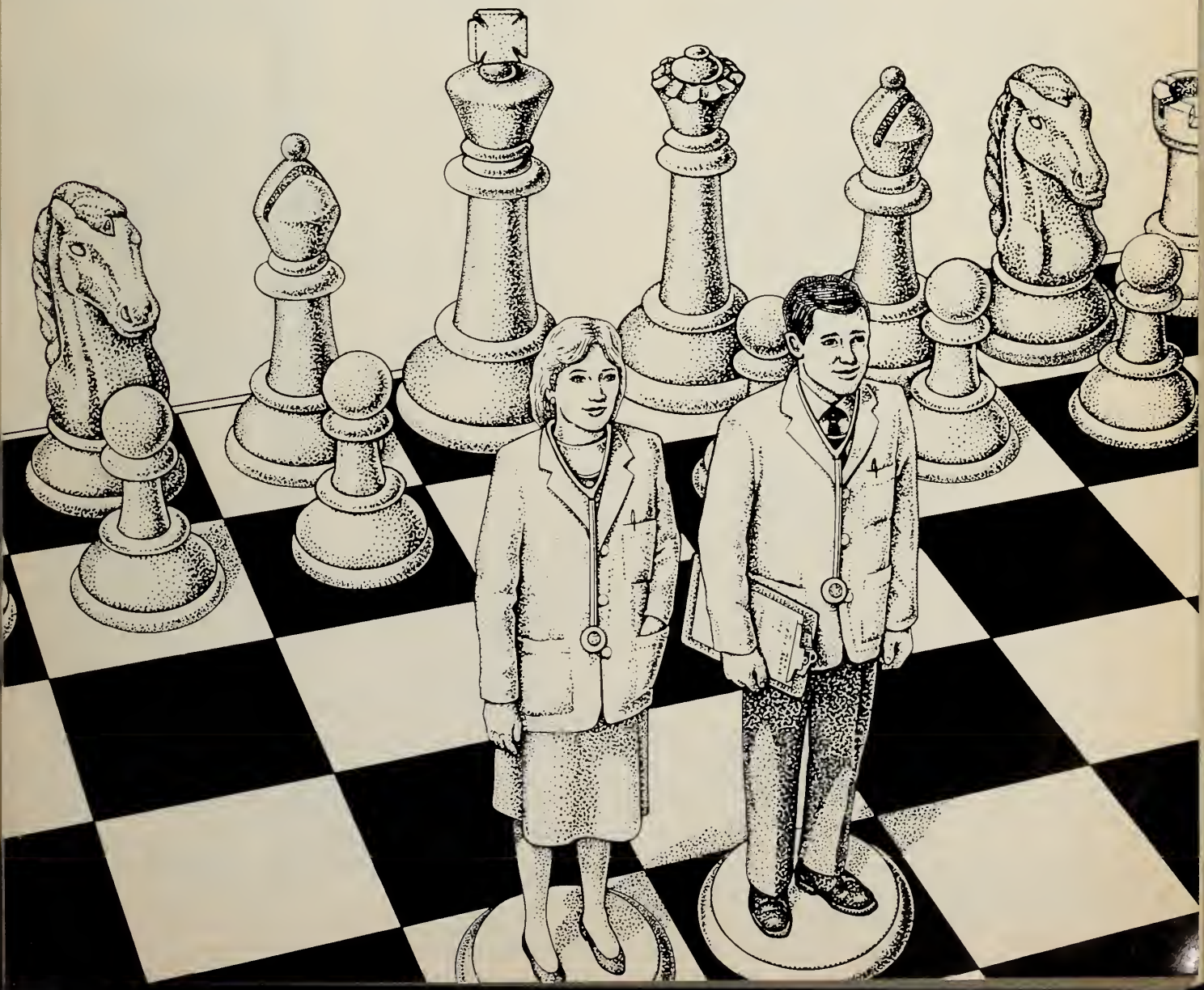

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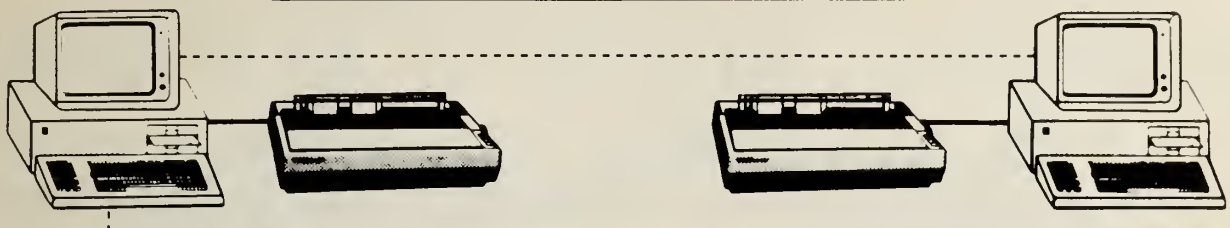

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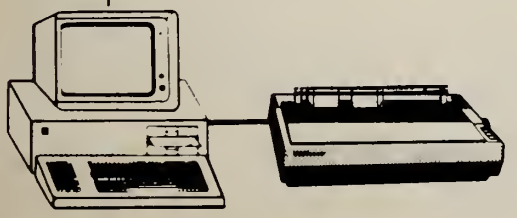

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FRIDAY, JANUARY 27, 1989

8:00 AM Registration and Coffee

8:45 AM *Welcome and Course Overview*
Jeffrey Balison, MD
WMS President

9:00-9:45 AM *Essentials of Assessment and Management of Trauma*
Joseph Primrose, MD

9:45-10:30 AM *Management of Shock*
Jeffrey Balison, MD

10:30 AM Coffee Break

10:45-12:00 NOON *Abdominal and Thoracic Trauma*
Merril Dayton, MD

12:00 NOON Luncheon Education Program
Trauma from Yellowstone Where the Buffalo Roam
Jeffrey Balison, MD

1:30-2:15 PM *Head Trauma*
James H. Johnson, Jr, MD

2:15-3:00 PM *Spine and Extremity Management*
John Bailey, MD

3:00 PM Coffee Break

3:15-3:45 PM *Recognition, Differential Diagnosis, Management of Delirium and Related Issues*
Oliver Cooperman, MD

3:45-4:45 PM *Pediatric Issues in Trauma*
J. Richard Hillman, MD

4:45 PM Adjourn

6:00-7:30 PM *President's Reception and Social Hour*
Hosted by The Doctors' Company

SATURDAY, JANUARY 28, 1989

8:30 AM Registration and Coffee

9:00-9:45 AM *Stabilization and Transport Issues: Complications of Tracheotomy and Airway Management*
Selvoy Fillerup, MD

9:45-10:30 AM *Air Transport of the Critically Ill or Injured Patient*
Richard Sugden, MD

10:30 AM Coffee Break

10:45-11:30 AM *Roundtable Discussion Summary and Wrapup of All Issues*
All Faculty Members

11:30 AM-approx. 1:30 PM *Presentation of Papers and Cases by WMS Members Followed by Question and Answer Period*

AUXILIARY

8:30-9:30 AM *Executive Committee*
Strategic Planning
All Members Invited

9:30-12:00 NOON General Session and Presentation by AMA Auxiliary President
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Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
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Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.
Administer cautiously to allergic patients.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever): 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%, genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology:
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis, elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 27-28—**Coronary Heart Disease Update.** Embassy Suites Hotel, Scottsdale. Fri-Sat. Contact: Deborah Wilderson, Medical Education Resources, 1 (800) 421-3756.

January 27-29—**Mammography and the Search for Breast Cancer.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Tess Wade, Breast Clinic of Rochester, (716) 442-8969.

January 28—**A Day of Hypertension.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

February 2-4—**1989 Risk Managed Emergency Medicine.** Fountains Suite Hotel, Phoenix. Thurs-Sat. Contact: Pam Lecheler, Emergency Physicians, Inc, (602) 870-0194.

February 10-15—**Laser and Stent Therapy in Vascular Disease: International Congress II.** The Phoenician Resort, Scottsdale. Fri-Wed. Contact: Becky Bowman, Congress Coordinator, (602) 955-1000.

February 22-24—**12th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

February 24-25—**Case Studies in ECG Interpretation and Arrhythmia Management.** Clarion Inn at McCormick Ranch, Scottsdale. Fri-Sat. Contact: Medical Education Collaborative, (303) 989-9802.

February 24-26—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Shay Southwick, AzAFP, (602) 249-2021.

February 28-March 3—**Pediatric Update 1989.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Barbara Bengtson, Phoenix Children's Hospital, (602) 239-4350.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

March 9-11—**Current Management of Central Nervous System Tumors.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1-800-BARROW-1.

March 30-April 1—**25th Annual Arizona Chest Symposium.** Westin LaPaloma, Tucson. Thurs-Sat. Contact: Susan Thornton, Tucson Medical Center, (602) 327-5461, ext 5110.

April 3-4—**Mayo Clinic Scottsdale Clinical Reviews.** The Registry Resort, Scottsdale. Mon-Tues. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

April 28-29—**Recent Advances in Cardiovascular Diseases.** The Registry Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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ANNUAL SESSION HIGHLIGHTS

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How to register:
ALL ACP MEMBERS: complete the registration materials in the Advance Program you received in December.

NON-MEMBERS: please look for a 12-page insert appearing February 1, 1989 in *Annals of Internal Medicine*, with a complete schedule of events and a registration form, or...call 1-800-523-1546, ext. 1229 [in PA, (215) 243-1200, ext. 1229].

PRE-REGISTRATION DEADLINE: February 27, 1989.

AMERICAN COLLEGE OF PHYSICIANS
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Philadelphia, PA 19104

A Time for Renewal

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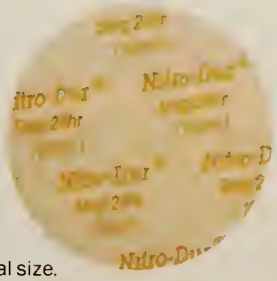

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CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription.

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CONTINUING MEDICAL EDUCATION

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January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sat-Sun. Contact: Murray G. Atnikov, MD. (604) 874-5291.

February 27-March 2—**17th Obstetric Anesthesia Conference.** Dept of Anesthesiology Ohio State at Sheraton Waikiki Hotel, Hawaii. Mon-Thurs. Contact: Arlene Rogers, Ohio State University Hospitals, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 16-19—**Obstetrical Anesthesia: 1989.** UCSF at Hotel Meridien, San Francisco. Thurs-Sun. Contact: Anita Edgecombe, UCSF, C 450, Box 0648, San Francisco 94143-0648. (415) 476-2273.

March 18-19—**34th Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

January 19-21—**Cardiology 89: New Pharmacology, New Procedures, New Pacemakers.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $300. Contact: Nancy Donegan, Deverman & Associates, 7777 Alvarado Rd, Ste 280, La Mesa 92041. (619) 668-9091.

January 28—**Selected Topics in Cardiovascular Medicine.** UCLA at Miramar Sheraton, Santa Monica. Sat. $35. Contact: UCLA.

February 15—**29th Annual Cardiology Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. Contact: Bonnie Wells, Enloe Hospital. (916) 891-7375.

February 24-25—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Grand Hotel, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 9-11—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at Maui, Hawaii. Thurs-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

March 10-11—**Risk Factors for Cardiovascular Disease: Lipids, Diabetes and Hypertension.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. $200. Contact: UCSF.

March 16-18—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Westin Maui Hotel. Thurs-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 31-April 1—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 14-15—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Las Vegas, Nevada. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

May 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Fisherman's Wharf. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

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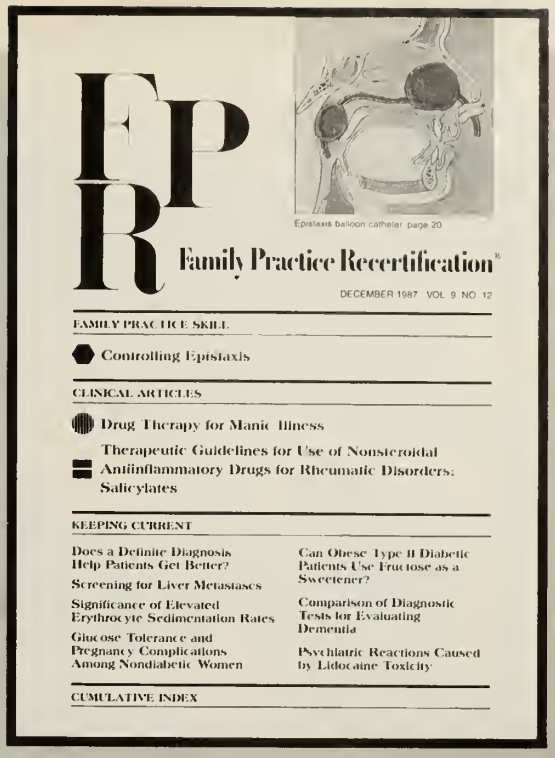
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CONTINUING MEDICAL EDUCATION

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DERMATOLOGY

June 2-3—**Southwestern Regional Cutaneous Flap Workshop.** UCLA Center for Health Sciences. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 26-30—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Maui Marriott, Maui, Hawaii. Thurs-Mon. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

March 2-5—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Sheraton Universal, Los Angeles. Thurs-Sun. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

April 5-7—**Advances in Emergency Medicine.** UCSF at Stanford Court, San Francisco. Wed-Fri. $380. Contact: UCSF.

April 26-28—**8th Annual Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Wed-Fri. 17 hrs. Contact: Orange County Trauma Society, 321 N Rampart, Ste 100, Orange 92668. (714) 937-5030.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 19-23—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 23-24—**Advanced Cardiac Life Support.** Center for Health Education at Long Beach. Fri-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 24-25—**11th Annual Poison Center Symposium: Emergency Medicine and Toxicology.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $280. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

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CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic	Petechiae, pruritus, photosensitivity, urticaria
Other	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use information before prescribing.

References: 1. Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frahlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whittle J, et al: Am J Cardiol 1982;49:554-559

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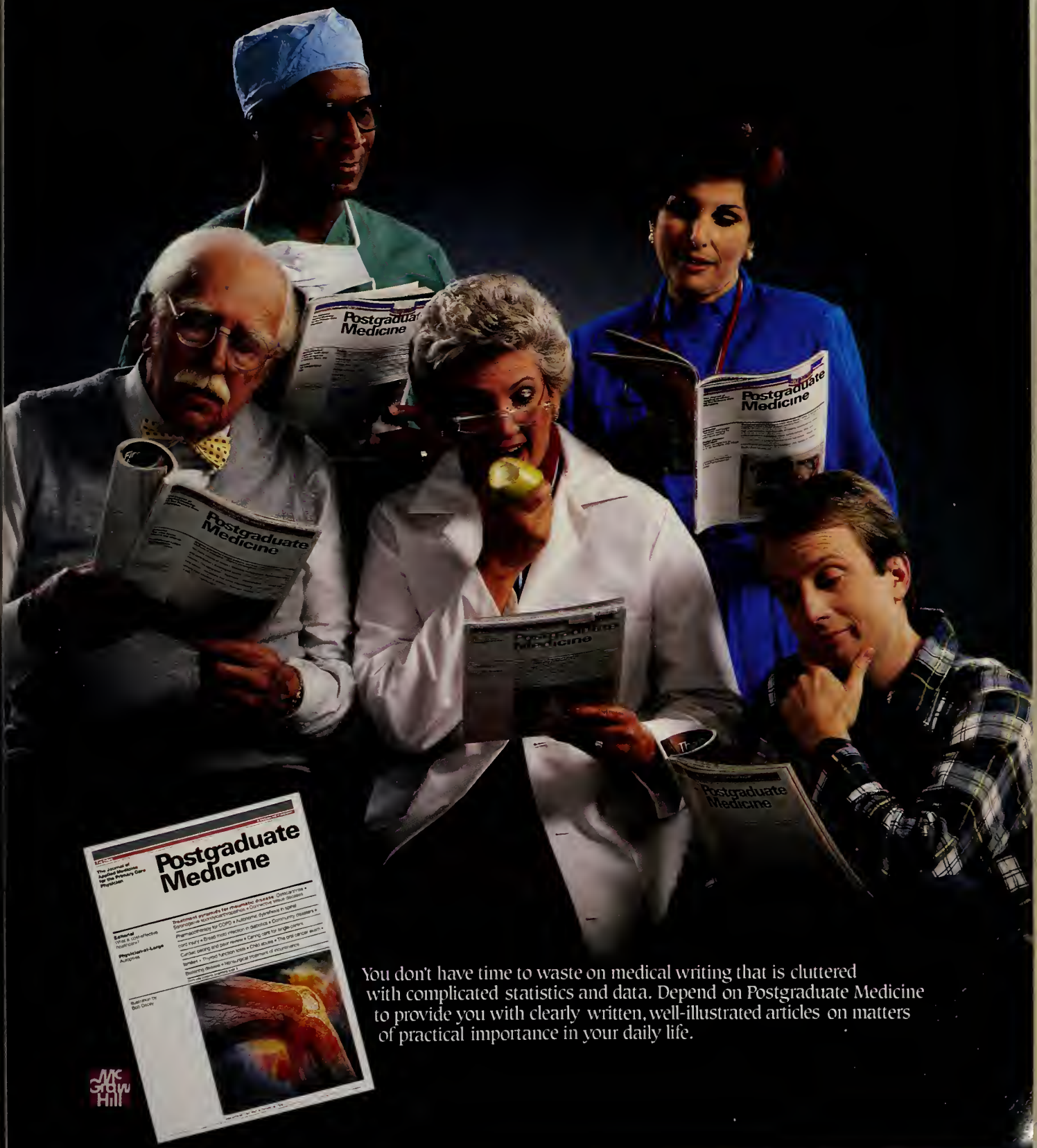

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CONTINUING MEDICAL EDUCATION

(Continued from Page 15)

INTERNAL MEDICINE

January-June—**Seminars in Cytopathology 1989.** UCSF at Health Sciences Room 300. Thurs/monthly. 12 hrs. $140 full series/$30 single. Contact: UCSF.

January 19-20—**Third Urological Symposium.** Kenneth Norris Jr Comprehensive Cancer Center at Moseley-Salvatori Conference Center, Los Angeles. Thurs-Fri. 12 hrs. Contact: Louise B. Ball, Executive Secretary, PO Box J, South Pasadena 91030. (213) 680-2387.

January 21—**Innovations in Ankle Arthroscopy.** Mount Zion Hospital and Medical Center at Hyatt Union Square, San Francisco. Sat. 7.25 hrs. $275. Contact: Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

January 23-26—**Neurology Update.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 25-27—**12th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wed-Fri. 21 hrs. $400. Contact: Edith S. Bookstein, NNN, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 8-10—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort, San Diego. Wed-Fri. 21 hrs. Contact: Bonny Mower, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 15-17—**22nd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15.5 hrs. $345. Contact: UCSF.

February 17-18—**Advances in Skin Cancer Management: A Multi-Specialty Approach.** UCSF at Ramada Renaissance Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

February 20-22—**Clinical Hematology and Oncology: 1989.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, Conference Coordinator. (619) 457-8556.

March 8-9—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square. Wed-Thurs. 14 hrs. $250. Contact: UCSF.

March 17-19—**Gastroenterology Update Cruise.** Center for Health Education at Queen Mary Hotel, Long Beach. Fri-Sun. Contact: Center for Health Education, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

March 17-23—**Internal Medicine 1989: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Fri-Thurs. 54 hrs. $495. Contact: Jacqueline Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 21-24—**Topics in Rheumatology II.** Straub Foundation at Ilikai Hotel, Honolulu, Hawaii. Tues-Fri. 16 hrs. $350. Contact: Juliana J. Woo, MPH, Straub Foundation, 846 S Hotel St, #302, Honolulu, HI 96813. (808) 524-6755.

April 14-15—**National Melanoma Conference.** Northern California Cancer Center and Melanoma Foundation at Sir Francis Drake Hotel, San Francisco. Fri-Sat. 9.25 hrs. $225. Contact: Chris Wagner, (415) 595-2704.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

OB/GYN

January 16-20—**21st Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 38 hrs. $595. Contact: USC.

January 29-February 3—**Changing Times in OB/GYN: Update 1989.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 24 hrs. $385. Contact: UCD.

March 10—**Contemporary Concepts in Reproductive Health Care: 1989.** Planned Parenthood/Alameda-San Francisco and UCSF at Merrit Peralta Health Education Center, Oakland. Fri. Contact: Marsha Gelt. (415) 441-7858.

March 15-18—**Horizons in Reproductive Health.** UCSD and Planned Parenthood/San Diego at Hotel del Coronado, San Diego. Wed-Sat. 15 hrs. $350. Contact: Carolyn Ferrer, Conference Coordinator, (619) 231-6760.

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

July 10-12—**Breastfeeding: A Natural World Resource.** La Leche League International at The Anaheim Hilton and Towers. Mon-Wed. 16 hrs. Contact: c/o La Leche League International, 9616 Minneapolis Ave, Franklin Park, IL 60131. (312) 455-7730.

OPHTHALMOLOGY

February 5-9—**8th Annual Squaw Valley Retinal Symposium.** Retina Faculty of UCD at Granibakken Resort, Tahoe City. Sun-Thurs. 16 hrs. $360. Contact: James W. Wells, Jr, MD, 3939 J St, Ste 210, Sacramento 95819. (916) 454-4861.

April 1—**Visions in Ophthalmology '89.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Sat. 5 hrs. $100. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

ORTHOPEDICS

January 21-28—**Orthopaedic Emergencies.** Scripps Memorial Hospital Encinitas at Kona Surf Resort, Kona, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 12—**1989 Interim Meeting of American Orthopaedic Society of Sports Medicine.** American Orthopaedics Society for Sports Medicine at Las Vegas, Nevada. Sun. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

PEDIATRICS

January 21—**Pediatric Cardiology for the Primary Care Physician.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Fri-Sat. 6 hrs. $75. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

January 27-29—**27th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott. Fri-Sun. 15 hrs. $225. Contact: Katherine Barky, MD, Childrens Hospital, PO Box 54700, Los Angeles 90054.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. 18 hrs. $220. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 15—**27th Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society at University Hilton Hotel, Los Angeles. Wed. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 18—**Management of Obstructive Airway Disease in Children: Interaction of the Pediatrician and Surgeon.** Los Angeles Pediatric Society at LAC-USC Medical Center. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 18—**Management of Congenital Urologic Problems in Children.** Los Angeles Pediatric Society at LAC-USC Medical Center. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 18—**Management of Pediatric Urologic Emergencies and New Techniques for Hypospadias.** Los Angeles Pediatric Society at LAC-USC Medical Center. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 20-22—**Pediatrics Update: 1989.** UCD at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 24-25—**California Conference on Health Care for Foster Children.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 14 hrs. $125. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 20)

March 9-11—**Brain Insults in Infants and Children: Diagnosis and Modern Management.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thurs-Sat. 15 hrs. $325. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 17-18—**Hematology and AIDS: Neonatal & Pediatric Perspectives II.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 12 hrs. $160. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 30-April 1—**Pediatric Trends.** American Academy of Pediatrics at Waiohai Hotel, Kauai, Hawaii. Thurs-Sat. 16 hrs. Contact: CME Registration, Department of Education, AAP, PO Box 927, Elk Grove Village, IL 60009-5005. (800) 433-9016.

April 15—**New Information on Old Exanthems.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Immunizations: Current and Future Vaccines.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Menstrual Problems in Adolescents.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Common Presentations of Uncommon Conditions; Uncommon Presentations of Common Conditions.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Atherosclerosis; Pathogenesis and Screening.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Hypertension in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Office Evaluation of Sports Injuries.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Fitness Training in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

January 22-27—**15th Annual Midwinter Program for Psychiatrists: Special Focus on Panic and Anxiety.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $385. Contact: UCD.

January 27-29—**New Advances in Cognitive Therapy.** UCSD at San Diego Marriott Hotel and Marina. Fri-Sun. 16 hrs. $375. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

RADIOLOGY

January 19-21—**Duplex Imaging.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sat. 16 hrs. $375. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

January 21-22—**Workshop on Percutaneous Disectomy.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Sat-Sun. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

January 23-25—**Neuroradiology Update 1989.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. 18 hrs. $375. Contact: Dawne Ryals, Ryals & Associates, (404) 641-9773.

January 23-27—**Combined Course—Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at San Diego Marriott Hotel and Marina, San Diego. Mon-Fri. 21 hrs. $450. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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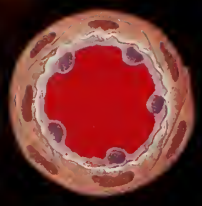
THE INSIDE/OUTSIDE STORY
IN HYPERTENSION

Effective peripheral vasodilation[1]



Undiminished cardiac output[2]

Undiminished renal function[3-5]

Uncompromised vitality

- ☐ Low incidence of fatigue and impotence[6,7]
- ☐ Undiminished exercise capacity[8]
- ☐ High level of patient acceptance

Effective blood pressure control

TRANDATE® *bid*

labetalol HCl/100 mg tablets

Because it vasodilates

Please see references and Brief Summary of Prescribing Information on adjacent page.

Allen & Hanburys™
Division of Glaxo Inc., Research Triangle Park, NC 27709

References: 1. Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75:24-31. 2. Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. 3. Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75(suppl 4A):103-108. 4. Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. 5. Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S. 6. Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:285-293. 7. Due DL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 8. Feit A, Holtzman R, Cohen M, et al: Effect of labetalol on exercise tolerance and double product in mild to moderate essential hypertension. *Am J Med* 1985;78:937-941.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will

TRANDATE® (labetalol hydrochloride) Tablets

be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat; laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

April 1988

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CONTINUING MEDICAL EDUCATION

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January 24-27—**MRI for Technologists—Symposium and Workshops.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Tues-Fri. 21 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

January 27-29—**41st Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 21 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

January 31-February 4—**15th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Westin Kauai, Hawaii. Tues-Sat. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 23-25—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Rancho Mirage. Thurs-Sat. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

February 24-26—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel Rancho Mirage, Palm Springs. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, Ryals & Associates, (404) 641-9773.

March 5-9—**Thoracic Imaging '89.** Society of Thoracic Radiology at Hotel Del Coronado, San Diego. Sun-Thurs. 32 hrs. $400. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

March 10-12—**Musculoskeletal Imaging: The State of the Art.** Hoag Memorial Hospital at Four Seasons Hotel, Newport Beach. Fri-Sun. 16 hrs. $375. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 16-21—**9th Annual San Diego Residents Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 28-30—**14th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

May 2-6—**9th Annual Mid-Pacific Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Royal Waikoloan Hotel, The Big Island of Hawaii. Tues-Sat. 19 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078

SURGERY

January-July—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 16-20—**12th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at U.S. Grant Hotel, San Diego. Mon-Fri. 26 hrs. $395. Contact: Nomi Feldman, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

January 27-29—**Annual Scientific Meeting of the Southern California Chapter American College of Surgeons.** American College of Surgeons at Palm Springs Riviera Hotel. Fri-Sun. Contact: SCACS, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581.

March 9-11—**Knee Reconstruction Surgery: ACL Repair, Patella Alignment and Total Knee Replacement.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Thurs-Sat. 30 hrs. Contact: Bonny Mower, Conference Coordinator, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 15-17—**Perioperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. $350. Contact: UCSF.

(Continued on Page 26)

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(Continued from Page 25)

March 16-19—**Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 6-8—**Postgraduate Course in General Surgery.** UCSF at San Francisco Hilton. Thurs-Sat. Contact: UCSF.

May 20—**6th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic Surgery Medical Group at La Jolla Marriott Hotel. Mon. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

OF INTEREST TO ALL PHYSICIANS

January 17-21—**Intensive Course in Geriatric Medicine.** UCLA Multi-Campus Division of Geriatric Medicine at Beverly Hilton, Beverly Hills. Tues-Sat. 34 hrs. $265. Contact: Susan Vivell, UCLA Multi-Campus Division of Geriatric Medicine, Dept 32-144 CHS, Los Angeles 90024-1686. (213) 825-8255.

January 18—**16th Annual Respiratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

January 19-22—**Health Science Response to Child Maltreatment: 1989.** Children's Hospital & Health Center at Omni Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 20-22—**Urology and Gynecology for Primary Care Physicians.** UCSD at Hyatt Islandia Hotel, San Diego. Fri-Sun. 13 hrs. Contact: Edith S. Bookstein, UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCD at San Diego Princess Resort. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 20-22—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at La Jolla Marriott. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Conference Coordinator, Department of Academic Affairs, 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

January 27-29—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Bally's Grand Hotel, Las Vegas. Fri-Sun. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

January 27-29—**New Drugs and New Indications.** UCSF at Granlibakken Resort, Lake Tahoe, Tahoe City. Fri-Sun. 15 hrs. $230. Contact: UCSF.

January 28-29—**Current Issues in Women's Health Care: Advances and Treatment Strategies.** American Medical Women's Association at Hotel Meridien Newport Beach. Sat-Sun. 10 hrs. $200. Contact: Deborah Mullaney or Darlene Mumm, Professional Communications. (213) 394-3322.

January 29-February 3—**Selected Topics in Family Practice.** Tropical Seminars at King Kamehameha Hotel, Kona, Hawaii. Sun-Fri. 20 hrs. Contact: Tropical Seminars, North Kitsap Medical Center, 20700 Bond Rd NE, Poulsbo, WA 98370-9099. (800) 441-4439.

February 1-4—**Recent Advances in Geriatric Medicine: Innovative Approaches to Quality Nursing Home Care: The Care Plan and Beyond.** UCSD at Catamaran Resort Hotel, San Diego. Wed-Sat. 17 hrs. $310. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121.

February 3—**Ionizing Radiation Safety.** USC. 2 hrs. Contact: USC. (213) 743-6383.

February 4—**Current Concepts in Medicine.** Los Angeles County Medical Association and Lancaster Community Hospital at Antelope Valley Inn Convention Center. Sat. 8 hrs. $65. Contact: Administrative Assistant, PO Box 2469, Lancaster 93539. (805) 945-0844.

February 10-12—**58th Midwinter Clinical Conference.** Research Study Club at Moseley-Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box J, South Pasadena 91030.

February 13-17—**Occupational Respiratory Protection.** USC. 3.5 hrs. Contact: USC. (213) 743-6523.

February 15-18—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 16-18—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and the Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

February 17-18—**A National Conference on Ethical Issues in the Care of Individuals with Handicapping Conditions.** North Bay Regional Center at Red Lion Inn, Rohnert Park. Fri-Sat. 10 hrs. Contact: Ethical Issues Conference, North Bay Regional Center, 1710 Soscol Ave, Napa 94559-0444. (707) 252-0444.

February 20-22—**9th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Perspective on Alcoholism Treatment: Ongoing Issues in Integrating the 12-Step Program.** Annenberg Center at Betty Ford Center at Eisenhower, Rancho Mirage. 13 hrs. Contact: Annenberg Center, Eisenhower Medical Center, 39000 Bob Hope Dr, Rancho Mirage 92270-3298. (800) 621-7322.

February 23-24—**Transportation of Hazardous Materials/Waste.** USC. 1.4 hrs. Contact: USC. (213) 743-6523.

February 25-March 4—**Update: Controversies in Emergency and Primary Care.** Scripps Memorial Hospital Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 27-28—**Back Injury Prevention.** USC. 1.4 hrs. Contact: USC. (213) 743-6523.

February 27-March 2—**Post Concussion Syndrome: Advances, Update and Review.** Centre for Neuro Skills and Southern California Neuropsychiatric Institute at Caesar's Palace, Las Vegas, Nevada. Mon-Thurs. 21 hrs. Contact: Sherry Ryan, SCNPI, La Jolla Blvd, La Jolla 92037. (619) 454-2102.

March 3-5—**Asia Pacific Alzheimer's Disease Conference.** Pacific Islands Geriatric Education Center at Hilton Hawaiian Village, Honolulu, Hawaii. Fri-Sun. 21 hrs. $300. Contact: Katherine Kim, Pacific Islands Geriatric Education Center, 347 N Kuakini St, Honolulu, HI 96817. (808) 523-8461.

March 3-5—**10th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Hyatt Regency, San Francisco. Wed-Fri. $365. Contact: UCSF.

March 4-5—**26th Annual Clinical Hypnosis Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Sat-Sun. 28 hrs. $350. Contact: Jan Brooks, 615-27th St, San Francisco 94131. (415) 826-0533.

March 5-8—**Asia-Pacific Osteoporosis Conference.** Kuakini Osteoporosis Center at Hilton Hawaiian Village, Honolulu, HI. Sun-Wed. 25 hrs. $450. Contact: Shirley Kuma, KOC, 347 N Kuakini St, Honolulu, HI 96817. (808) 547-9578.

March 8—**Veterinary Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

March 8-10—**9th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF Department of Radiation Oncology at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF. (415) 595-2704.

March 10-12—**Current Concepts on the Pathogenesis and Treatment of Allergic Diseases.** Allergy Foundation of Northern California at Hyatt Lake Tahoe, Nevada. Fri-Sun. 9 hrs. $90. Contact: Professional Communications, (213) 394-3322.

March 10-12—**Controversies in Cholesterol and Aging.** Marin Medical Society and Heart Association at Sonoma Mission Inn & Spa, Sonoma. Fri-Sun. 12 hrs. $325. Contact: Peggy Page, Marin Medical Society, (415) 924-3891.

March 18-19—**26th Annual Clinical Hypnosis Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Sat-Sun. 28 hrs. $350. Contact: Jan Brooks, 615-27th St, San Francisco 94131. (415) 826-0533.

March 18-25—**Primary Care Medicine: Update '89.** UCSF at the Waiohoi, Kauai, Hawaii. 1 week. 20 hrs. $465. Contact: UCSF.

March 19-22—**Annual Meeting of the Society for Adolescent Medicine.** Society for Adolescent Medicine at San Francisco. Sun-Wed. Contact: Edie Moore, 10727 White Oak Ave, Ste 101, Granada Hills 91344. (818) 368-5996.

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(Continued from Page 26)

March 29-31—**Annual Review in Family Medicine: Pharmacotherapeutics in Primary Care.** USC at Stanford Court Hotel, San Francisco. Wed-Fri. 14 hrs. Contact: Department of Family and Community Medicine, 400 Parnassus Ave, A C9, San Francisco 94143-0900. (415) 476-5250.

April 1-2—**New Drugs and New Indications.** UCSF at Cole Hall. Sat-Sun. 15 hrs. $230. Contact: UCSF.

April 8—**Antibiotics: 1989 and Beyond.** Grossmont District Hospital at Kona Kai and Tennis Resort, San Diego. Sat. 8 hrs. Contact: Verda Belyeu, CME Office, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

April 12—**Preventive Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

April 12-14—**39th Annual Course for Physicians in Family Practice: Family Practice Update 1989.** Mount Zion Hospital and Medical Center at San Francisco. Wed-Fri. $325. Contact: Family Practice Course, Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

April 13-15—**Recent Advances in Hemophilia Care.** The Hemophilia Treatment Center Orthopaedic Hospital at Los Angeles Hilton. Thurs-Sat. $200. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 14-16—**Office Orthopaedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 29-30—**The Cutting Edge 1989 Erotic Mysteries: Resolving Obstacles to Intimacy.** UCSD at San Diego Marriott Hotel & Marina. Sat-Sun. 12.5 hrs. $295. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 30-May 3—**12th Annual National Conference on Rural Health: Redesigning Rural Health: Blueprints for Success.** National Rural Health Association at Bally's Hotel, Reno, Nevada. Sun-Wed. Contact: Robert Quick, Communications Director. (816) 756-3140.

May 10—**Laboratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

June 4-9—**The Power of the Art: Humanism, Healing and Health Care.** Kauai Foundation for Continuing Education and The Hawaii Medical Association at Poipu Beach, Kauai. Sun-Fri. 25 hrs. $395. Contact: David J. Elpern, MD, 3420-B, Kuhio Highway, Lihue, HI 97666. (808) 245-5653.

IDAHO

March 23-24—**Infectious Diseases of the Lung—Idaho Thoracic Society Annual Meeting.** Anderson Center, Boise. Thurs-Fri. Fee: $20, ITS members; $40, nonmembers. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 21-22—**Family Practice Winter Seminar.** Journal Center Pyramid Holiday Inn, Albuquerque. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

March 1-4—**New Mexico Metabolism Symposium.** Quail Ridge Inn, Taos. Contact: Kathy Sikes, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

March 2-4—**Santa Fe Ski Symposium—The Kidney in Systemic Disease.** Hotel Eldorado, Santa Fe. Contact: Pat Scott, National Kidney Foundation of NM, 1715 Girard NE, Albuquerque 87106. (505) 266-4573.

March 4—**Common Gastrointestinal Problems of Children.** UNM Nursing/Pharmacy Building, Room 135, Albuquerque. Contact: New Mexico Pediatric Society, UNM School of Medicine, Dept of Pediatrics, Albuquerque 87131. (505) 277-3967.

March 9-11—**Orthopaedic Surgery Conference.** Tammaron at Purgatory. Contact: Kathy Sikes, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 6-8—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). Fri-Sun. 15 hrs. Snowbird. Contact: (801) 581-8664.

January 12-14—**Arthroscopic Surgery** (Sponsor: UUMC). Thurs-Sat. Phoenician Resort, Scottsdale, Arizona. Contact: (801) 581-7601.

January 14-21—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). One week. Aston Genesis Resort, Park City. Contact: (801) 581-8664.

January 21—**Leland R. Cowan Cancer Symposium** (Sponsor: LDSH). Sat. University Park Hotel, Salt Lake City. Contact: (801) 321-1854.

January 25-28—**Health/Life Planning: Caring for the Difficult Patient** (Sponsor: UUMC). Wed-Sat. Salt Lake City. Contact: (801) 521-2645.

February 1-4—**Rigid Fixation and Craniofacial Anomalies** (Sponsor: UUMC). Wed-Sat. Snowbird. Contact: (801) 581-8664.

February 5-10—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird. Contact: (801) 581-7553.

(Continued on Page 30)

SPECIAL ISSUES

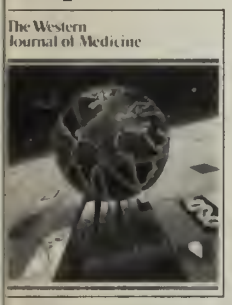
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

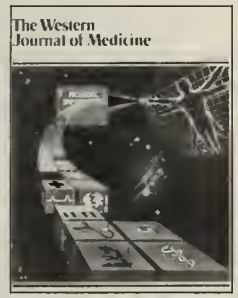
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



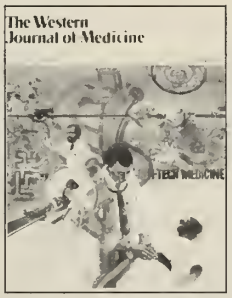
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



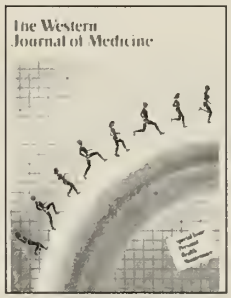
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



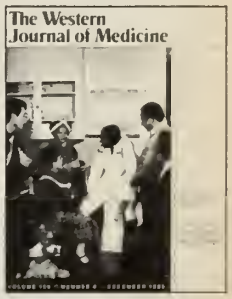
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 28)

February 7-10—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Red Lion Inn, Salt Lake City. Contact: (801) 581-8635.

February 12-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. The Yarrow, Park City. Contact: (801) 581-8664.

February 20-24—**Fifth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. Park City. Contact: (801) 379-7178.

February 22-25—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott. Contact: (801) 521-1311.

February 22-25—**Rigid Fixation and Craniofacial Anomalies** (Sponsor: UUMC). Wed-Sat. Snowbird. Contact: (801) 581-8664.

February 22-25—**Health/Life Planning: Caring for the Difficult Patient** (Sponsor: UUMC). Wed-Sat. Scottsdale. Contact: (801) 521-2645.

February 25-March 1—**30th Annual OB/GYN Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 521-5501.

February 26-March 3—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: (801) 581-7553.

March 1-4—**Update in Maternal Fetal Medicine** (Sponsor: UUMC). Wed-Sat. Contact: (801) 581-5501.

March 6-10—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

March 8-11—**Health/Life Planning: Caring for the Difficult Patient** (Sponsor: UUMC). Wed-Sat. St George. Contact: (801) 521-2645.

March 17—**Update in Infectious Diseases** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, Salt Lake City. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 13—**Understanding Arrhythmias & Pacemakers: A Workshop for Practitioners.** Seattle. Fri. Contact: VMMC.

January 26-27—**Advances in Cardiology and Cardiac Surgery.** Seattle. Thurs-Fri. Contact: U/W.

February 1-3—**Aging and Elderly.** Seattle. Wed-Fri. Contact: U/W.

February 3—**Advances in Therapy of Hypertension.** Seattle. Fri. Contact: VMMC.

February 9-10—**Legal Aspects of Occupational Safety and Health.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

February 10-11, May 19-20, August 24-25—**MKSP Review Course, Parts 1, 2, 3.** Seattle. Fri-Sat. May: Fri-Sat. Aug: Thurs-Fri. Contact: VMMC.

February 17-18—**Primary Care Orthopedics.** Seattle. Fri-Sat. Contact: U/W.

February 27-March 1—**Current Issues in Infectious Disease.** Seattle. Mon-Wed. Contact: (206) 326-7349.

March 3—**Neurologic Complications of Systemic Disease.** Seattle. Fri. Contact: VMMC.

March 10—**Management of Problem Wounds.** Seattle. Fri. Contact: VMMC.

March 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: U/W, (206) 543-1069.

March 13-23—**PM&R Review.** Seattle. Mon-Thurs. Contact: U/W.

March 20-24—**Drug Therapy.** Maui. Mon-Fri. Contact: U/W.

March 22-24—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

April 20-21—**Ergonomics.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069.

May 18-19—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

June 1-3—**International Symposium on Pediatric NeuroOncology.** Seattle. Thurs-Sat. Contact: U/W.

June 2—**Current Otology.** Seattle. Fri. Contact: VMMC.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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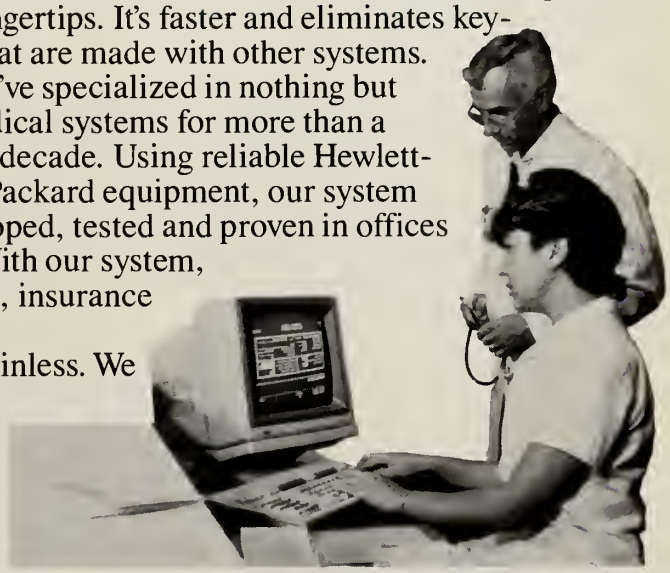

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This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.

Warnings: Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.

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Clinical Investigation

Use of the Kinetic Treatment Table to Prevent the Pulmonary Complications of Multiple Trauma

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The kinetic treatment table (KTT) has been developed to prevent and treat complications of immobility. Because atelectasis and pneumonia may be related to immobility, we studied the effect of the KTT on the prevention and treatment of pulmonary complications in a prospective randomized study of 30 patients with severe traumatic injuries. All were receiving mechanical ventilation and were randomly assigned to treatment with a KTT or a conventional bed. Both groups received conventional medical-surgical therapy while pulmonary function, chest roentgenograms, and the presence or absence of lung infection were monitored for one week. In the patients who began the study with a clear chest roentgenogram, atelectasis and pneumonia were significantly less frequent in those treated with a KTT ($P < .05$). Thus, the KTT can reduce pulmonary complications in selected patients with multiple trauma. The effect of this benefit on overall outcome is uncertain.

(Demarest GB, Schmidt-Nowara WW, Vance LW, et al: Use of the kinetic treatment table to prevent the pulmonary complications of multiple trauma. West J Med 1989 Jan; 150:35-38)

Atelectasis and pneumonia are frequent complications in trauma victims, especially those immobilized by their injuries.[1-8] An oscillating bed has been developed to reduce the complications resulting from immobility, including pulmonary complications. This bed, the Rotorest Kinetic Treatment Table (KTT; Kinetic Concepts, San Antonio, Texas), provides nearly absolute skeletal stability while rotating a patient through a maximum range of 120 degrees every 3½ minutes. Although the KTT is being used increasingly in intensive care units, the indications for its use have not been well defined. Because trauma victims are often immobilized early in their hospital course, treatment directed at this immobility may reduce pulmonary complications. To investigate this hypothesis, we carried out a randomized prospective study of the effect of the KTT on the incidence of atelectasis and pneumonia in patients with multiple trauma.

Patients and Methods

Patient Selection

Patients admitted to the University of New Mexico (Albuquerque) Medical Center trauma unit were considered for the study if they were adult, if because of their injuries they were expected to be immobilized for at least three days, and if at least 50% of their lung fields were normal by chest roentgenography. The study was conducted in the 18 months from November 1984 through April 1986. If the attending physician agreed with the use of either the kinetic treatment table or a conventional bed for one week, the patient was recruited for the study and informed consent was obtained. The patient was assigned to treatment with the KTT or a conventional bed by using a blinded randomizing scheme, which assigned an equal number of patients to each treatment in groups of eight. After reviewing the cases of the first 32 patients, we determined that the treatment appeared effective in those patients who began the study with normal chest roentgenograms. Recruitment was then restricted to patients with normal chest roentgenograms, and, by this process, five additional patients were studied.

Of the 32 patients enrolled initially, 7 were excluded from analysis. Four patients were excluded because their participation in the study was terminated in less than three days, one because of an exacerbation of underlying injuries, and three because of rapid improvement. Two patients were excluded because data at the end of the study were insufficient to evaluate outcome. A seventh patient was excluded because his injury was a burn in contrast to the traumatic injuries sustained by the rest of the group.

Treatment

During the study period, all patients received the usual intensive care by medical and nursing staffs. Patients in conventional beds were turned from side to side every two hours as their injuries permitted. Patients on the KTT were rotated continuously except when nursing duties, diagnostic tests, or therapies required the rotation to be temporarily suspended. All patients were encouraged to sit up and ambulate as soon as possible. Participation was for one week, but the study was terminated earlier if patients were able to move sooner.

Data Collection and Analysis

A member of the study team made daily clinical observations. Injuries were catalogued and classified using a stan-

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dard scale.[9] Data collected included maximum temperature per 24-hour period, the presence and gross appearance of sputum, and various aspects of a patient's respiratory state, including indicators of ventilator support. Arterial blood gas values were determined and chest x-ray films taken as clinically indicated. In patients treated with the KTT, the hours of active rotation were noted. All chest roentgenograms from entry to completion of the study were reviewed systematically by two of us (A.R.A., L.W.V.). The location and extent of opacities were noted according to the position on the anteroposterior film.

For the purpose of analysis, oxygenation was assessed by the ratio of the arterial oxygen pressure to inspired oxygen fraction, mechanical ventilation was classified according to the degree of support, and chest roentgenograms were classified by the extent of abnormality. Pneumonia was diagnosed when purulent sputum and any parenchymal opacity on a chest roentgenogram were present and the patient had a temperature greater than 38.5°C (101.3°F). Comparisons between groups were done using the *t* test for continuous data and Fisher's exact test for categorical data. A *P* value of less than .05 was considered significant.

Results

Of the 30 patients available for analysis, 16 were assigned to a KTT and 14 to a conventional bed (Table 1). Sex, age, and injury severity scores were similar in both groups. The types of surgical procedures were different in the two groups; craniotomy was more common among patients using the KTT, and abdominal operations were more common in the control group.

The frequency and extent of pulmonary abnormalities were similar in each group at the start of the study (Table 2). Respiratory failure, assessed by the amount of mechanical ventilatory support and the degree of hypoxemia, was not significantly different. Admission chest x-ray films were abnormal and pneumonia was present in similar proportions in each group.

These patients represent a select group. The requirement that patients be eligible for treatment in either bed created a major obstacle to patient recruitment. That is, the neurosurgical staff did not provide patients who had cervical spine injuries because they thought that all patients with this diagnosis should be treated with the kinetic treatment table. The requirement that immobilization be anticipated for at least three days further narrowed the possibilities. Most patients with minor injuries, including many with closed head trauma, were excluded. The injuries of the participants were extensive, and all patients were receiving mechanical ventilatory assistance at the beginning of the study.

Patients selected for the kinetic treatment table started rotation as soon after admission as was practical, on average 1.9 days (range 0 to 6 days) after admission. The average rotation time was 12.2 hours (range 7.1 to 16.3 hours) per day. No complications were associated with rotation.

There was no difference in outcome when the two treatment groups were compared. Mortality rates were similar: Eight patients in the KTT group and six in the control group died. Length of stay in the intensive care unit was not significantly different—15.1 days for the KTT group and 11.4 days in the control group. The pulmonary status at the end of the study was similar in both groups (Table 2). Recovery from respiratory failure occurred at the same rate in both groups. The frequency of mechanical ventilatory assistance and degrees of hypoxemia were similar at the end of the observation period. More chest roentgenograms were clear in the KTT group than in the control group, but the overall distributions of abnormality in both groups were not significantly different. Furthermore, when chest roentgenograms taken at the end of the study were compared with those taken on admission, the groups had a similar number of improved, unchanged, or worsened cases. In addition, a similar number in each treatment group had pneumonia at the end of the study.

Because prophylaxis of pulmonary complications was a major study objective, the subset of patients who had clear chest x-ray films at the start of the study was examined separately (Table 3). Nine patients treated with the KTT and six with a conventional bed had clear chest films at the begin-

TABLE 1.—*Clinical Features of Patients Assigned to the Kinetic Treatment Table (KTT) and of Control Patients*

Clinical Feature	*KTT Patients n=16*	*Control Patients n=14*
Sex, M/F	14/2	13/1
Age (mean/range), yr	39.5 (18-76)	36.9 (16-77)
ISS (mean/range)	29.4 (16-57)	27.9 (13-57)
Injuries*		
Head and face	11	12
Spine	1	0
Chest	5	10
Abdomen	3	8
Extremities	5	11
Operations*		
Head	15	2
Thoracic	3	1
Abdominal	10	16
Orthopedic	6	7
Tracheostomy	10	6
Other	3	1

ISS=injury severity score

*Some patients had injury and surgical treatment of multiple sites.

TABLE 2.—*Pulmonary Status—All Patients**

Pulmonary Variable	*KTT Patients, n=16*		*Control Patients, n=14*	
Time of Study	*Start*	*End*	*Start*	*End*
Pa_{O_2}:Fi_{O_2}, mean ± SEM	*224±20*	*217±23*	*266±28*	*245±22*
	Patients, No.			
Ventilator score				
Spontaneous breathing	0	7	0	6
Mechanical ventilation <10 liters/min	2	4	0	2
Mechanical ventilation >10 liters/min	12	4	12	6
Mechanical ventilation >10 liters/min + PEEP >10 cm H_2O	2	1	2	0
Chest x-ray film				
Clear	9	10	6	3
Opacity in 1 lobe	1	1	4	6
Opacity in 2 lobes	3	1	3	3
Opacity in 3 or more lobes	3	4	1	2
Pneumonia	6	6	4	8

Fi_{O_2}=fraction of inspired oxygen, KTT=kinetic treatment table, Pa_{O_2}=partial pressure of arterial oxygen, PEEP=positive end-expiratory pressure, SEM=standard error of the mean

*All KTT/control comparisons are not statistically significant.

ning. At the end of the study, only one patient treated with a KTT had an abnormal chest film, and this was associated with pneumonia. In contrast, five of six patients treated in a conventional bed had roentgenographic opacities, and four had pneumonia. Despite the small numbers, these differences were significant. The injury severity score, oxygenation, and frequency of mechanical ventilation at the beginning and the end of the study were not different in these two subsets.

Discussion

The purpose of this study was to evaluate the prophylaxis of pulmonary complications in immobilized trauma patients by the early use of the kinetic treatment table. Significantly less atelectasis or pneumonia developed in patients who entered the study with roentgenographically clear lungs when they were treated with the KTT. Patients with abnormalities in their lungs at the beginning of the study, however, received no benefit from using the KTT in terms of further progression or resolution of atelectasis or pneumonia. Furthermore, in all patients, the degree of respiratory failure, duration of intensive care, and mortality were not affected by the KTT. Thus, while using the KTT reduces the incidence of pulmonary complications in selected patients, its importance in the patients' overall outcome is uncertain.

The conclusions of this study are limited by several aspects of the study's design. Because our patients were a highly selected group, our findings and conclusions apply only to patients with similar injuries. Excluding patients with cervical spine injuries, in particular, may have prejudiced the study because a previous investigation has shown benefit in this group.[10] Also, it is possible that immobilized patients with less extensive injuries or patients not requiring mechanical ventilation may have shown a greater benefit from the KTT. The one-week period of treatment and observation may have affected the findings. Our study was restricted to a week because of practical constraints and because we expected respiratory complications to develop early in the illness, as was the case in a series of patients with respiratory failure due to neuromuscular disease.[11] While a week is probably adequate to evaluate prevention, it may be too short a period to examine recovery from atelectasis and especially from pneumonia. In the study of neuromuscular disease and respiratory failure, a diminishing of roentgenographic abnormalities was not observed until two to four weeks after their appearance.[11] Implementing the KTT earlier in the course and a greater rotation time may have produced a greater benefit. The logistics, however, of caring for severely traumatized patients limit the use of the KTT especially within the first several days, when frequent trips to diagnostic and operating suites occupy much of the time. Finally, the absence of a significant difference for most comparisons between our treatment groups may be attributed to the relatively small sample size. Thus, our study does not exclude a small treatment effect of the KTT, but we do not think a small effect is clinically important.

Previous retrospective studies of the use of the KTT have shown its protective effect against pulmonary complications. In a review of a 42-month experience with the KTT in patients with acute spinal cord trauma, Green and co-workers showed that atelectasis or pneumonia developed in only 2 of 105 patients.[12] Pneumonia and atelectasis developed in only 9 of 162 quadriplegic and paraplegic trauma victims.[13] Brackett and Condon found a 25% incidence of pulmonary complications in quadriplegics immobilized on the KTT compared with a 69% incidence in patients treated in the previous five-year period with a Stryker frame.[10] Although none of these studies were done with concurrent control cases or random assignment to control treatment, the low incidence of pulmonary complications is impressive and certainly lower than the incidence of complication in this study. This discrepancy may be explained by differences in the extent of injury and the frequency of respiratory failure in the respective groups. It is noteworthy that in this study, the patients who began treatment without pulmonary complication had a low frequency of complication a week later similar to that of other studies of the KTT.[10,12,13]

The decision to use the kinetic treatment table in patients with immobility due to trauma requires a consideration of the potential risk of pulmonary complication versus the limited benefit of the KTT. The table does offer some short-term advantage when initiated before pulmonary complication has occurred, but it is uncertain whether this benefit is important for the ultimate outcome. Thus, in patients with trauma and respiratory failure already treated with mechanical ventilation, the additional benefit of the KTT appears to be limited.

TABLE 3.—*Pulmonary Status—Patients With Clear Admission Chest Roentgenograms*

Pulmonary Variable	*KTT Patients, n=9*		*Control Patients, n=6*	
Time of Study	*Start*	*End*	*Start*	*End*
Pa_{O_2}:Fi_{O_2}, mean ± SEM	*287±17*	*254±30*	*334±51*	*254±35*
	Patients, No.			
Ventilator score				
Spontaneous breathing	0	5	0	2
Mechanical ventilation <10 liters/min	2	3	0	2
Mechanical ventilation >10 liters/min	7	1	5	2
Mechanical ventilation >10 liters/min + PEEP ≥10 cm H_2O	0	0	1	0
Chest x-ray film*				
Clear	9	8	6	1
Opacity in 1 lobe	0	0	0	3
Opacity in 2 lobes	0	1	0	2
Opacity in 3 or more lobes	0	0	0	0
Pneumonia*	0	1	0	4

Fi_{O_2}=fraction of inspired oxygen, KTT=kinetic treatment table, Pa_{O_2}=partial pressure of arterial oxygen, PEEP=positive end-expiratory pressure, SEM=standard error of the mean

*Chest x-ray films were more frequently abnormal and pneumonia more frequent in control group at end of study, $P<.05$.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

The Quarterback Speaks to His God

Herbert Wilner. Cayuse Press, PO Box 9086, Berkeley, CA 94709, 1987. 239 pages, $17.95.

The call for a humane point of view in contemporary medicine has rarely been sounded with more eloquence and urgency than in this collection of stories by Herbert Wilner, an extraordinarily gifted writer and teacher at San Francisco State University who died in 1977. We are all dying, of course, but not with the Angel of Death perched so conspicuously on our shoulder, as was the case for Wilner during the entire last decade of his brief life. Inadvertently victimized by zealous radiotherapy, his cancer was cured at the expense of an inexorably progressive constrictive pericarditis. The world of illness became his dark forest of intimate concern. This book reflects Wilner's knowledge of the meanings and experiences of illness, and the revelations of the human condition that emerged for him. Thus, these tales juxtapose courage and fear, cruelty and altruism, fierce clinging to life and the seemingly casual renunciations of suicide.

The quick intimacy of hospital roommates is the centerpiece of several stories: the sharing of family tales and joshing cut short by the terrible experience of bearing helpless witness to another's suffering. Other stories detail the desperate and lonely preoccupations that attend the anticipation of surgery, the aftereffects of therapeutic failure, and the triumph of the human spirit in locating options for choice where none seem to exist. The latter theme unfolds in a brilliantly crafted tragicomic story of an impaired woman who comes to realize just moments before the operation that will restore her hearing that it will also undo the delicate balance of her difficult marriage. Deafness is a requirement of certain adaptations. With that insight and without a word to anyone, she packs her few belongings, walks out of her room, out of the hospital, and back into her newly chosen previous life. The threat of surgery had worked an unusual magic. Another classic tale explores the moral dilemma of wishing for the death of a terminally ill parent. The sharp edge of this conflict is cut by a selfless hospital aide who feeds and encourages his elderly charge as the son knows he should but cannot. The effects of troubled history are too powerful.

The ordeal of preparing for the corrective operation from which Wilner never recovered is compellingly told in the story that bears the title of this collection. "The Quarterback Speaks to His God" is a metaphor for the unfolding exposure of courage and character in Wilner's battle with death and dying. Here he draws the reader into the experiential world of the cardiac invalid where fear and boredom battle fatigue for attention. The illness is as real a character in the life of the protagonist, an ex-football hero, as is his wife. Like a jealous mistress his disease deprives her of consort as thoroughly as it robs him of every form of appetite. Respite comes in brief moments of sweet recall, but the elegant details of relived mastery on the playing field evaporate before the commanding minutiae of incipient arrhythmia. "Like the scurryings under his breastbone of a tiny creature with scrawny limbs . . . there's chaos in his heart. Following a wild will of its own, it has nothing to do with him, nor can he do anything with it."

In the final analysis it is not death but dying that is so difficult. And when the space between life and death narrows, the living can take on its most intense forms. Those forms manifest literally beneath our very medical noses but are rarely seen by us. Although we battle not to "switch off," there is little evidence that the importance of maintaining a primary concern with the whole patient has been secured. Every marvelous advance in the diagnostic and therapeutic sciences seems to obscure rather than sharpen our perceptions of the emotional and spiritual aspects of illness and treatment. Wilner's book is a powerful antidote for the potentially toxic influences in our progressively technologized and third-party-involved practice of contemporary medicine. What a great loss it would be if the wisdom imbedded in Wilner's fine writing should go unnoticed by the medical profession and be wasted on us. This reviewer hopes for a different fate for this remarkable collection and recommends it as required reading, most especially for those who are certain that they are too busy to read it.

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Clinical Medicine

Needle Biopsy of the Liver

A Critique of Four Currently Available Methods

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There are currently four needle biopsy methods for obtaining tissue from patients with possible diffuse liver disease or cancer. These include percutaneous blind needle biopsy, a visually guided needle biopsy at laparoscopy, guided fine-needle biopsies with ultrasonography or computed tomography, and the transvenous liver biopsy. We and others have found the guided fine-needle biopsy technique to be safe, relatively cheap, and highly accurate in the diagnosis of liver cancer. Blind percutaneous biopsy should be reserved for patients with possible diffuse, noncancerous, liver disease. Guided biopsies at laparoscopy can be done if the other two methods fail to give a tissue diagnosis. The transvenous approach is useful in patients with a coagulation disorder.

(Babb RR, Jackman RJ: Needle biopsy of the liver—A critique of four currently available methods. West J Med 1989 Jan; 150:39-42)

The pathologic interpretation of liver tissue obtained by needle biopsy has become increasingly important in diagnosing liver disease. Initially, tissue was obtained with the use of relatively large needles inserted blindly into the liver through a transthoracic or subcostal approach.[1] This technique has subsequently been modified, and needles are now 1.2 to 2.0 mm in diameter.[2,3] Although this blind approach has been accurate in diagnosing most diffuse liver diseases,[4-9] it has been a disappointment in the evaluation of primary and metastatic liver cancer.[8,10,11] Thus, over the past decade the use of guided needle biopsies has become increasingly popular.[12] Currently, there are four methods available for needle biopsy of the liver (Table 1): the percutaneous, blind transthoracic or subcostal approach; the guided biopsy under direct vision at the time of laparoscopy; the guided fine-needle biopsy or aspiration using modern radiographic techniques; and the transvenous or transjugular biopsy. We will evaluate these four methods, discuss their strengths and weaknesses, and propose guidelines for their appropriate use.

Percutaneous, Blind Needle Biopsy

Over the past 50 years, the standard method for obtaining liver tissue has been the percutaneous transthoracic or subcostal needle biopsy.[1] Various needles are available today; the most popular ones have a diameter of 1.2 to 1.6 mm. As currently done, the procedure is safe with a mortality rate less than 0.02%,[1] and it can be accomplished in an outpatient setting if a hospital support system is nearby.[13,14] Although numerous complications may occur, such as pain, hypotension, bile leakage, bacteremia, and unintentional biopsy of other abdominal organs, these are uncommon and rarely have serious sequelae.[1] The most feared complication is hemorrhage, but when the biopsy is done carefully with the smallest possible needle in patients without a coagulation disorder, the incidence is less than 1%.[13-15]

If a possibility of diffuse liver disease such as alcoholic hepatitis, acute or chronic viral hepatitis, or fatty liver is the reason for the biopsy, the results have been accurate.[4,7-9] The small core of tissue representing 1/50,000 of total liver mass is representative of the entire liver.[16] Moreover, intraobserver and interobserver variations among pathologists in interpreting the biopsy specimens have been low, and the interpretation of various possible histologic features of specimens is satisfactory.[6,17]

Diagnosing cirrhosis may be difficult using the percutaneous needle biopsy. Its diagnostic accuracy has varied from less than 50% to 96%.[18] This has been attributed to inadequate size of the specimen, tissue fragmentation, the biopsy needle glancing off hard fibrous tissue, and irregular spacing of macronodules.[18,19] Goldner took biopsy specimens from cirrhotic livers at autopsy using three different needles.[20] The specimens obtained using a TruCut needle with a diameter of 2.0 mm were more accurate for cirrhosis than those taken with the 1.6-mm Menghini and Klatskin needles. Abdi and co-workers did biopsies in 118 patients with suspected liver disease just before autopsy.[8] A Klatskin needle was used, and three separate passes were made. Cirrhosis was diagnosed in only 80% of the first biopsy specimens. Maharaj and associates likewise did biopsies in 75 patients three times using a TruCut needle.[11] Only 50% showed cirrhosis on all three biopsy specimens. Soloway and colleagues did multiple biopsies at the same time using a Vim-Silverman needle on 50 patients with chronic hepatitis.[6] Only three of seven with cirrhosis had features of the same in all biopsy specimens. Over a one- to three-year period, repeat biopsy specimens showed no signs of cirrhosis in six patients having it on the initial biopsy.

A common indication for needle biopsy of the liver has been a suggestion of primary or metastatic cancer. Review of the literature shows an overall sensitivity of about 70% to 75% with a range of 66% to 90%.[10,16] The accuracy of the blind needle biopsy in this setting has been increased by doing two biopsies rather than one[16] and by including cyto-

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
FNB = fine-needle biopsy

logic techniques rather than histologic examination alone.[21,22] As might be expected, the biopsy success rate correlates with the amount of cancer in the liver. Conn and Yesner[10] found 21% of liver biopsy specimens to be "positive" if one to three metastatic nodules were present compared with 100% accuracy when the liver was at least 50% replaced by cancer. It is clear that a blind needle biopsy occasionally, if not often, misses liver cancer.

Guided Needle Biopsy at Laparoscopy

Guided needle biopsies of the liver may be done under direct vision using the technique of laparoscopy.[23] After local anesthesia and sedation, or general anesthesia, nitrous oxide or carbon dioxide is introduced into the patient's abdomen producing a pneumoperitoneum. The abdominal cavity and its contents can then be visualized through a telescope passed through a cannula in the anterior abdominal wall. A biopsy can be taken of suggestive areas on the liver surface under direct vision. The overall complication rate is less than 1% and mortality less than 0.03%.[23,24]

As noted above, the blind percutaneous needle biopsy is accurate in diagnosing diffuse liver disease. Picciotto and co-workers carried out three liver biopsies each on 60 patients with nonfocal liver disease.[25] The first was done by the percutaneous method, and the other two were done at laparoscopy. The results were the same in 57 of the 60 patients, the only variability being in the severity of chronic hepatitis in 3 patients. Czaja and associates did percutaneous blind and guided needle biopsies at laparoscopy in 36 cadavers.[9] There was no difference between the two in the diagnosis of diffuse liver disease. In a review of the literature, Nord[19] found laparoscopic biopsy to be more accurate than percutaneous needle biopsy with regard to cirrhosis.

It has been estimated that 90% of liver cancers are visible at laparoscopy[24]; thus, a guided needle biopsy should be accurate. Results show an accuracy of 80% to 95%, which is considerably higher than for the blind percutaneous biopsy technique.[23,24]

Jori and Peschile in 1972[26] compared the results of blind needle liver biopsy with laparoscopy in 48 patients with possible liver cancer. On blind biopsy, the results in 14 of 20 patients (70%) with primary liver cancer and in 5 of 16 (31%) with metastatic cancer were abnormal ("positive"). The guided needle biopsy at laparoscopy showed abnormalities in 19 of 20 (95%) with primary liver cancer and 14 of 16 (88%) with metastatic disease. In the cadaver study noted above, Czaja and colleagues found that of five patients with liver cancer, one was diagnosed with the blind percutaneous biopsy in contrast to four at laparoscopy (biopsy and visual inspection).[9] In 28 patients suspected of having liver cancer, Friedman and Wolff were able to establish a positive tissue diagnosis in 25 using guided biopsies at laparoscopy.[27] The liver could not be adequately visualized in the other three patients. The results of a prior blind percutaneous needle biopsy had been falsely normal in 6 of these 25 patients. Lightdale found that of 60 patients with documented liver cancer at laparoscopy, 23 had previously normal results on a blind liver biopsy.[24]

Brady and co-workers have recently compared the results of needle biopsy in patients with focal liver disease using either a computed tomography (CT) or laparoscopic-guided technique.[28] Of 12 patients with liver cancer randomly assigned to the CT group, biopsy specimens showed abnormalities in 9 (80%). Laparoscopic-guided biopsies showed abnormalities in six patients with cancer; the examination was inadequate in two others, one of whom later was shown to have metastatic liver disease. An additional 19 patients thought to have liver disease with a normal CT scan underwent laparoscopy. Four were found to have malignant lesions. The authors concluded that these two techniques of guided liver biopsies were equally satifactory in patients with focal liver lesions.

TABLE 1.—*Cost of Liver Needle Biopsy*

	Cost, $
Percutaneous needle biopsy	
Room and monitoring charge	400
Physician's fee	150
Pathology (hospital)*	200
Total	750
Guided needle biopsy at laparoscopy	
Room and monitoring charge	600
Physician's fee	800
Pathology (hospital)*	200
Total	1,600
Guided needle biopsy with ultrasonography	
Ultrasound procedure	160
Pathology (clinic)†	88
Total	248
Guided needle biopsy with computed tomography (CT)	
CT procedure	300
Pathology (clinic)†	88
Total	388
Transvenous needle biopsy (inpatients only)	
Biopsy procedure	500
Equipment charge	160
Pathology (hospital)*	200
Total	960

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Guided Fine-Needle Biopsy With Ultrasonography or Computed Tomography

Over the past ten years it has become increasingly clear that percutaneous fine-needle biopsy (FNB) of the liver with guidance by ultrasonography[29] or computed tomography[30] is both accurate and safe. With the use of these imaging techniques, thin-walled needles of 0.6 to 0.9 mm in diameter can be directed into focal liver lesions. The aspirated specimen contains cells mixed with blood and tissue fluid that can be sent for cytologic and histologic examination.[31]

The accuracy of this technique in various series for the diagnosis of liver cancer ranges from 80% to 99%,[32-51] much higher than with percutaneous blind needle biopsy. Although the aspirated material may be sent for cytologic or histologic evaluation, many authors[35-37,41,45,46,49,50] have found a higher yield for cancer when both are done on the same specimen. Four reports[29,38,40,52] have noted many examples of FNB results showing cancer in patients having had a prior percutaneous liver biopsy with normal findings. False-positive results are uncommon, having been reported in only 3 of the 21

articles surveyed. The incidence was 1/49,[36] 2/130,[45] and 1/92[51] patients.

Because the needles used are of small caliber and can be guided away from adjacent organs or vascular structures, FNB is safe. In 1971 Lundquist reported only one serious complication in 2,611 aspirations.[53] In numerous reports since that time,[32-51] few if any serious complications were found even when hemangiomas were accidentally punctured.[39,44,45] The overall complication rate is 0% to 2.4%, with a death being extremely rare.[48]

In the future, guided needle biopsies may be done using the Biopty-Cut Biopsy Needle (C.R. Bard Inc). With this method a core of tissue is obtained, rather than aspirated cells. Experience with the use of this instrument for liver biopsy is currently limited in the United States.

Transvenous Liver Biopsy

The above methods of liver biopsy may be contraindicated in some patients with liver disease because of a coagulation disorder. In this setting, the transvenous liver biopsy method may be helpful. After a catheter is introduced and guided through an internal jugular vein and subsequently through the vena cava system into a hepatic vein, a biopsy needle is inserted through the catheter and then into the hepatic tissue using a suction technique.[54,55] In a recent review from France,[54] tissue was obtained in 1,000 of 1,033 attempts (96.8%). If there was no hepatic fibrosis, the tissue specimen obtained was adequate for diagnosis in 191 of 193 cases (98.9%); if there was fibrosis or cirrhosis, however, the tissue was adequate in only 518 of 807 cases (64%). Rosch and co-workers obtained adequate specimens in 39 of 44 attempts.[55] This method of liver biopsy appears to be safe and workable when done by experienced operators.

Discussion

Currently, as discussed above, physicians can choose between four methods of obtaining tissue by needle biopsy in the diagnosis of diffuse or focal liver disease. Each can be considered well established and not experimental. As noted in Table 1, the cost differs for each procedure.

If diffuse liver disease is suggested, such as acute or chronic hepatitis, steatosis, or cirrhosis, the blind percutaneous liver biopsy should be done. More tissue is required for diagnosis than can be obtained with FNB, and there is no advantage to a guided needle biopsy at laparoscopy.[9,25] If the results of a blind percutaneous biopsy are normal and yet cirrhosis is suspected, the next procedure may be laparoscopy.[19]

Patients with possible liver cancer should have FNB under either ultrasonographic or CT guidance. This technique is quick, safe, can be done in an outpatient setting, and compares favorably in cost with the other two methods. Multiple aspirations can be done and the specimens sent for both cytologic and histologic examination. The degree of accuracy for focal liver cancer is higher with FNB than with the percutaneous blind biopsy, approaching 90% in most studies.[32-51] We would reserve laparoscopy for patients in whom FNB and percutaneous blind biopsies have failed and yet the suspicion of liver cancer remains high, or for situations where it is important to know if cancer has spread to other parts of the abdomen or peritoneum. Finally, in patients with a coagulation disorder, the transvenous method can be used.[54,55]

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Simple Treatment for Chronic Female Infections

ABOUT A THIRD OF WOMEN who come to see me have seen an average of four physicians previously and have had therapy for a chronic yeast infection. The trouble is, they do not have an infection at all; they have a mucositis due to some sort of irritating substance. I will just make one generalization: If a substance is colored, if it has a fragrance, or if it is alkaline, it is bad news for the vaginal mucous membrane. And, I think, as a general rule, you can treat these patients symptomatically with acidification and drying.

I have my patients—when they bathe or shower—wash the soap film off the vulvar and vaginal skin surfaces carefully, and dry themselves off thoroughly with a soft cotton towel. Then I have them use a hair dryer to dry off the vulva, the intertriginous area, so that they are dry, and then have them powder themselves with cornstarch or baby powder. I think cornstarch is preferable because it does not have a fragrance. And, again, if it has a fragrance, there is a potential for it to be an allergen.

Having the patient use a hair dryer and cornstarch, a washing routine, and acidification with boric acid means that you may never find out what the nature of the problem was, but I guarantee that you will make these patients more comfortable.

There are some potential irritants that you should be taking specific histories about. Opulent soaps are the absolute chief offender. What I recommend is white Dove soap. Another thing that I want to just remind you about is colored toilet paper. The first question for women with persistent urethritis is: What color is the toilet paper in your bathroom? If it is blue, have them change it. And again you will be amazed, and I think you will be gratified, with how some of these seemingly unsolvable mysteries can be solved by considering fairly mundane things: perfumes, spermicides, spermicidal jellies, chlorinated pools, feminine hygiene sprays, deodorant tampons.

I think it is important to discuss candidly with your patients issues like their masturbation habits or whether they have anal intercourse. A substantial proportion of women with recurrent nonspecific bacterial vaginosis who stop having anal intercourse do not have bacterial vaginosis anymore.

—JOHN H. GROSSMAN III, MD

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Usefulness of Endomyocardial Biopsy in Tertiary Care

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Over a 51-month period, 143 patients underwent right ventricular endomyocardial biopsy as part of their evaluation for cardiac disease. Of these, 82 patients presented with a clinical dilated cardiomyopathy, 28 patients with unexplained arrhythmia, 22 with other cardiomyopathies, 7 with anthracycline exposure, and 4 with miscellaneous indications. Overall, 47 of the 143 patients (33%) had findings on endomyocardial biopsy that changed the clinical diagnosis. Of these, 18 (38%) had a change in diagnosis based on nonspecific criteria. Although 32 of the 143 patients (22%) had specific therapeutic alterations based on the endomyocardial biopsy findings, the vast majority of these received immunosuppression for myocarditis, a therapy that is currently of unproven benefit. Therefore, endomyocardial biopsy is of limited therapeutic use for most patients with primary myocardial disease. Its current primary indications are for clinical diagnosis and investigation.

(Hosenpud JD: Usefulness of endomyocardial biopsy in tertiary care. West J Med 1989 Jan; 150:43-45)

Endomyocardial biopsy has been reported as an aid to the diagnosis of several disease states involving the myocardium.[1] A diagnostic study should, however, either provide new information or its results should somehow influence therapeutic decisions, or both. An endomyocardial biopsy is an invasive procedure that is costly and not without risk.[2] Its overall usefulness in providing the above-stated goals has rarely been rigorously analyzed.[3] Accordingly, the records of all patients undergoing endomyocardial biopsy for various indications (excluding cardiac transplant follow-up) were analyzed retrospectively to determine whether the results of the procedure influenced subsequent care.

Patients and Methods

The records of all patients undergoing an endomyocardial biopsy from September 1982 to February 1987 were reviewed. If a patient had more than one biopsy for follow-up of a specific disease, only the first biopsy done for an initial diagnosis was used in the analysis. A specific indication category was chosen at the time of the biopsy procedure in all instances and noted on the request for pathologic evaluation. This indication category also determined the quantity of tissue taken, the fixative used, and the specific stains required, if any. The specific indication categories were dilated cardiomyopathy (rule out myocarditis); hypertrophic cardiomyopathy; restrictive cardiomyopathy; indeterminate cardiomyopathy (unable to classify); unexplained arrhythmia (no obvious structural heart disease); anthracycline therapy; and other, where specific indications not falling into other categories were noted.

Following receipt of the final pathologic interpretation, the medical record was reviewed and the following additional data were acquired: duration of and specific symptoms, physical findings, medications, laboratory studies including invasive and noninvasive cardiac function studies if done, final diagnosis, and the presence of a therapeutic manipulation based on biopsy findings.

The final pathologic report was used for data analysis. All endomyocardial biopsies were evaluated for the presence of inflammation, necrosis, hypertrophy, fibrosis, and myocardial cell nuclear atypia. In addition, abnormalities such as amyloid deposition were noted if specific stains were indicated by the clinical presentation. Cardiomyopathic changes were considered present when fibrosis, hypertrophy, and nuclear atypia were noted.[4] A diagnosis of chronic lymphocytic myocarditis was made if both lymphocytic infiltrate and myocardial cell necrosis were present, based on long-standing criteria of this institution and as more recently suggested by Aretz and colleagues.[5] A specific number of lymphocytes per area of myocardium was not used in making the diagnosis of myocarditis. Myocardial damage due to anthracycline toxicity (intracellular vacuolization and myofibrillar loss) was graded from 0 to 3 based on criteria developed by Billingham and co-workers.[6] Other specific disease processes were based on standard pathologic criteria.

The specific indications, clinical characteristics, pathologic diagnosis, final diagnosis, and specific therapy, if any, were then analyzed. A change in clinical diagnosis would include the following: myocarditis in a patient with dilated cardiomyopathy, cardiomyopathy in a patient with unexplained arrhythmias, amyloidosis or other specific disease process in a patient with a nonetiologic diagnosis such as restrictive or hypertrophic cardiomyopathy. Biopsy-directed therapy would include the following: immunosuppression for myocardial inflammation; alteration in the anthracycline dose based on biopsy findings; exclusion from other therapies because of biopsy findings, such as excluding from heart transplantation or a more extensive evaluation because of amyloid deposition in the myocardium.

Statistical differences between groups of patients were

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determined using Student's *t* test for nonpaired data and Fisher's exact test where appropriate. Significance was considered present at a *P* value of less than .05.

Results

During the study period, 143 patients underwent an endomyocardial biopsy using the Caves-Schultz bioptome. Their ages ranged from 12 to 72 years (mean 43 years), and symptom duration ranged from 1 day to 312 months (mean 23 months). Although 19 patients underwent more than one biopsy for follow-up of their specific disease process, only the first biopsy from these patients was used in this analysis. Table 1 shows the number of patients and percentage of the group undergoing biopsy for each specific indication. The two most common indications at this institution were clinically dilated cardiomyopathy of unknown etiology and unexplained arrhythmia. Complications related to the endomyocardial biopsy were few and included myocardial perforation (3%), pneumothorax, asymptomatic air embolism, and supraventricular arrhythmias (each 1%). Nearly all of the complications occurred in the first 25 procedures done, consistent with a learning curve, and there were no deaths related to the procedure.

Table 2 shows the pathologic diagnoses made by biopsy for the entire group. The most frequent diagnosis was cardiomyopathy, with myocarditis the second most frequent. Only 16 patients had completely normal results.

Of the 82 patients who presented with a clinically dilated cardiomyopathy, 22 showed histologic evidence of myocardial inflammation (chronic lymphocytic myocarditis). Figure 1 summarizes the clinical and hemodynamic findings of patients with dilated cardiomyopathy with and without myocardial inflammation. In this series, patients with myocarditis were significantly younger, had a shorter symptom duration, and had a more equal male-to-female incidence compared with those with dilated cardiomyopathy. Also, the mean heart rate was significantly faster and left ventricular chamber size smaller in those with myocarditis on biopsy.

Table 3 summarizes those cases in which, as a result of the endomyocardial biopsy, the diagnosis was changed. In all, 47 new diagnoses were made by endomyocardial biopsy.

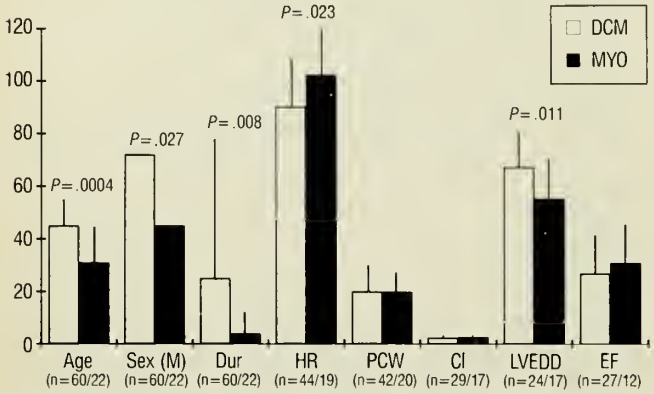

Figure 1.—The graph shows clinical and hemodynamic variables in patients with dilated cardiomyopathy (DCM; white bars) and myocarditis (MYO; black bars). Sex (M) = percentage of male patients, Dur = symptom duration in months, HR = heart rate (beats per minute), PCW = pulmonary wedge pressure (mm of mercury), CI = cardiac index (liters/min/m^2), LVEDD = echo left ventricular end-diastolic dimension (mm), EF = ejection fraction (%), n = cohort size for DCM/MYO for each variable measured. Results are expressed as mean ± 1 standard deviation.

Included in this total were 18 patients with unexplained arrhythmias who had changes consistent with but not diagnostic of cardiomyopathy. In support of a diffuse myocardial process in these 18 patients was their reduced ejection fractions (0.54 ± 0.20) and elevated pulmonary wedge pressures (14 ± 10 mm of mercury).

Table 4 summarizes those cases in which, as a result of the biopsy, there was a change in therapy. As shown, 32 patients underwent specific changes in their therapeutic regimen based on the results of the endocardial biopsy. Of these 32 patients, 24 received immunosuppression for a biopsy diagnosis of myocarditis, a currently unproven mode of

TABLE 1.—*Indications for Endomyocardial Biopsy*

Indication	*Patients* Number	*Patients* Percent
Dilated cardiomyopathy	82	57
Unexplained arrhythmia	28	20
Restrictive cardiomyopathy	9	6
Indeterminate cardiomyopathy	8	6
Anthracycline therapy	7	5
Hypertrophic cardiomyopathy	5	3
Other	4	3
Total	143	100

TABLE 2.—*Pathologic Diagnoses From Myocardial Biopsy*

Diagnosis	*Patients* Number	*Patients* Percent
Cardiomyopathy	90	63
Lymphocytic myocarditis	24	17
Giant cell myocarditis	2	1
Anthracycline toxicity	4	3
Amyloidosis	2	1
Vasculitis	1	1
Normal histology	16	11
Indeterminate or inadequate	4	3
Total	143	100

TABLE 3.—*Patients in Whom Biopsy Findings Altered Diagnosis*

Clinical Diagnosis	*Biopsy Diagnosis*	*Patients, Number*
Dilated cardiomyopathy		82
	Myocarditis	22
Unexplained arrhythmia		28
	Cardiomyopathy	18
	Myocarditis	2
	Granulomatous myocarditis	2
	Arteritis	1
Restrictive cardiomyopathy		9
	Amyloidosis	2

TABLE 4.—*Patients in Whom Biopsy Findings Altered Treatment*

Biopsy Diagnosis	*Therapeutic Intervention*	*Patients, Number*
Myocarditis	Azathioprine and prednisone	22
Granulomatous myocarditis	Prednisone	2
Anthracycline toxicity	Alteration of dose	7
Amyloidosis	No heart transplant	1

therapy. Eliminating these patients would leave a total of only eight patients who had a clinically justifiable change in therapy. Seven of these eight underwent a biopsy specifically for a therapeutic decision (anthracycline therapy). The other patient was referred for cardiac transplantation with a "hypertrophic" cardiomyopathy. Amyloidosis was unexpectedly discovered on endomyocardial biopsy, and the patient was therefore felt not to be a candidate for transplantation.

Discussion

Transvenous endomyocardial biopsy was first reported by Sakakibara and Konno in 1962.[7] Its use as a routine cardiologic diagnostic tool was limited, however, until the early 1970s when endomyocardial biopsy became the method of choice for following cases of cardiac allograft rejection.[8] It was not until after 1980, in response to a report by Mason and associates,[9] that endomyocardial biopsy gained favor for evaluating primary myocardial disease. The specific use was in patients with dilated cardiomyopathy to rule out myocarditis. It has also been used to evaluate anthracycline toxicity,[6] to define other forms of cardiomyopathy,[10,11] and to evaluate patients with unexplained arrhythmias, of whom a high percentage will have unexpected pathologic disease.[12-14] Several reviews of the procedure outline the diagnoses that can and have been made using endomyocardial biopsy.[1,15,16] Only rarely have these reports specifically determined the incidence of diagnostic findings, even less often the impact of the diagnostic findings on patient care.[3]

A recent editorial by Mason suggests that the role of endomyocardial biopsy will be limited to searching for "needles in a haystack."[17] The current analytic study supports these conclusions. Although 33% of the patients had a biopsy-caused change in diagnosis, of this subgroup, more than a third—those with arrhythmia as an indication—had the diagnosis of cardiomyopathy made on the basis of fairly nonspecific histologic findings,[4] and their presence in the general population is unknown. The findings of reduced ejection fractions and elevated filling pressures in this subgroup support the diagnosis and may have prognostic implications.

The other large group in whom a biopsy changed the diagnosis were those with myocarditis. This is likely a legitimate diagnostic category, as the prognosis in these patients may differ considerably from that in patients without myocardial inflammation.[18] As can be seen by the clinical characteristics between those with and without inflammation, the diagnosis must be made histologically. The benefit of a specific intervention for myocarditis is still unproved,[19] and the diagnostic criteria used in making a diagnosis of myocarditis are open to debate even among experienced pathologists.[5,20,21]

What, then, are firm indications for an endomyocardial biopsy? The least controversial indication not addressed in this series is to diagnose rejection in a cardiac allograft.[8] Other well-documented indications include monitoring for anthracycline cardiac toxicity[6] and the diagnosis of specific although uncommon myocardial or systemic diseases such as amyloidosis, hemochromatosis, and sarcoidosis.[10,22,23]

A less firm indication is for those patients with a recently occurring dilated cardiomyopathy to rule out myocarditis. This approach may be justifiable from a prognostic standpoint,[18] although this is controversial.[24] In addition, there are data from studies in animals to suggest that exercise during active myocardial inflammation may exacerbate myocardial dysfunction.[25,26] It is hoped that specific therapy will ultimately be available for myocarditis, further justifying the need for a specific diagnosis.

Finally, there appears to be a high incidence of unsuspected myocardial disease in patients with normal cardiac function and unexplained arrhythmias.[12-14] Although, again, in most cases specific therapy is not available, there may be important prognostic implications to the biopsy findings.

If therapeutic intervention is the only justification for a diagnostic procedure, then endomyocardial biopsy today has relatively few absolute indications. Endomyocardial biopsy, however, has provided and, it is hoped, will continue to provide new information for better understanding and classification of primary myocardial diseases. This must occur before a specific therapy can be forthcoming.

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Ethnic Differences in Mortality From Acute Rheumatic Fever and Chronic Rheumatic Heart Disease in New Mexico, 1958-1982

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To examine time trends and differences in mortality rates from acute rheumatic fever and chronic rheumatic heart disease in New Mexico's Hispanic, American Indian, and non-Hispanic white populations, we analyzed vital records data for 1958 through 1982. Age-adjusted mortality rates for acute rheumatic fever were low and showed no consistent temporal trends among the three ethnic groups over the study period. Age-adjusted and age-specific mortality rates for chronic rheumatic heart disease in Hispanic and non-Hispanic whites decreased over the 25-year period, although rates were higher among Hispanics than among non-Hispanics during most of the time period. In American Indians, age-adjusted mortality rates for chronic rheumatic heart disease increased between 1968 and 1977 to twice the non-Indian mortality rates during the same period. Despite this increase in mortality from chronic rheumatic heart disease among New Mexico's American Indians from 1968 to 1977, the New Mexico data generally reflect national trends of decreasing mortality from chronic rheumatic heart disease.

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Although acute rheumatic fever and chronic rheumatic heart disease were once major public health problems in the United States, dramatic decreases in their incidence and prevalence have taken place over the past 50 years.[1-4] The reasons for this national decline remain a matter of speculation,[1] but changes in host factors, alterations in the virulence of the streptococci, disappearance of a necessary cofactor in the production of disease, and an increasing use of antibiotic therapy for pharyngitis may have been responsible.[1,3,5] Socioeconomic factors and changing social conditions have also been considered important in the nationwide decline of acute rheumatic fever and chronic rheumatic heart disease.[1,6] Not all racial groups have experienced this decline to the same extent.[7-12] A higher incidence of acute rheumatic fever has been documented in blacks,[10,11] American Indians,[7] Hawaiians,[8] US Samoans,[8] and Hispanics[12]; these elevations in disease incidence have been attributed primarily to less favorable living conditions associated with lower economic status.

New Mexico has three major ethnic groups—Hispanics, American Indians, and non-Hispanic whites—each with unique social systems and health beliefs and with widely divergent socioeconomic characteristics. Of New Mexico's American Indians, 41% live below the poverty level—as do 23% of Hispanics—compared with only 10% of the state's non-Hispanic whites.[13] The Indian and Hispanic populations also have fewer years of formal education than do the non-Hispanic whites in the state.[13] Although strong ethnic differences have been observed for cancer incidence and mortality in New Mexico,[14,15] as well as for other diseases, ethnic differences in the epidemiology of acute rheumatic fever and chronic rheumatic heart disease have not been examined. The rationale for examining these diseases derives from the differing cultural characteristics of Hispanics, American Indians, and non-Hispanic whites as these characteristics may affect disease-specific morbidity and mortality rates.

In this report we describe the epidemiology of mortality from acute rheumatic fever and chronic rheumatic heart disease in New Mexico's three major ethnic groups, Hispanics, American Indians, and non-Hispanic whites. We have examined vital records for the period 1958 to 1982 to characterize time trends in mortality from these diseases and have calculated age-adjusted and age-specific mortality rates by sex and ethnic group for New Mexico's culturally diverse residents.

Subjects and Methods

We obtained coded death certificate data for New Mexico residents for the years 1958 to 1982 from the New Mexico Bureau of Vital Statistics. The cause of death on the certificates was coded according to the seventh revision of the International Classification of Diseases (ICD) for the years 1958 to 1968,[16] the eighth ICD revision for the years 1969 to 1978,[17] and the ninth ICD revision for the years 1979 to 1982.[18] Deaths attributed to acute rheumatic fever were

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coded as ICD 400 to 402.9 in the ICD seventh revision and as 390 to 392.9 in the eighth and ninth revisions. Deaths attributed to chronic rheumatic heart disease were coded as 410 to 416.9 in the seventh revision and as 393 to 398.9 in the eighth and ninth revisions.

The ethnicity of persons was assigned by the Bureau of Vital Statistics on the basis of information contained on the death certificates. Hispanic ethnicity was determined on the basis of the decedent's surname, the surnames of the decedent's parents, and specific statements on the death certificate. American Indians were identified solely on the basis of information cited on the death certificate. American Indian cases were primarily reported among the state's Navajo, Pueblo, Zuni, and Apache tribes. Non-Hispanic whites were coded as "white" on the death certificate and did not have a Spanish surname or other information to indicate that they were Hispanic. Because of a small number of cases, we did not examine mortality from acute rheumatic fever and chronic rheumatic heart disease among blacks or other ethnic or racial groups.

Denominators for rate calculations were derived from the censuses of 1960,[19-21] 1970,[22-24] and 1980 (Table 1).[13] Because different techniques were used by the US Census Bureau to identify ethnicity, we have adjusted the estimates of the Hispanic white population from 1960 to 1980 to account for the different enumeration procedures.[25] To clarify the comparability of the different techniques in determining ethnicity, we conducted a cross-sectional survey of Hispanics and non-Hispanics in New Mexico in which each of the ethnic identifiers from the censuses of 1960, 1970, and 1980 was included in a single questionnaire. The responses obtained in this survey provide rough guidelines of the comparability of the Hispanic data from the three censuses. We adjusted the estimates of the Hispanic populations from the 1960 and 1970 censuses on the basis of this survey.[25] Estimates of the American Indian population for 1960 were adjusted to account for systematic errors that occurred in data processing.[26]

Age-specific and age-adjusted mortality rates were calculated for the five-year periods, 1958-1962, 1963-1967, 1968-1972, 1973-1977, and 1978-1982. Age-adjusted rates were calculated by the direct method and standardized to the 1970 standard-million population of the United States. Age-specific and age-adjusted mortality rates were similarly calculated for the single years from 1958 to 1982 to assess temporal trends.

We used standard programs from the Statistical Analysis System[27] for our analyses.

Results

Age-adjusted mortality rates by time period for acute rheumatic fever and for chronic rheumatic heart disease are shown in Tables 2 and 3. In New Mexican male and female subjects, decreases in chronic rheumatic heart disease-related mortality rates were apparent in Hispanics and in non-Hispanic whites from 1958 to 1982, with the most dramatic decreases observed among Hispanic women. An increase in chronic rheumatic heart disease-related mortality was observed in American Indian men and women from 1968 to 1977. During this ten-year period, mortality rates for American Indians were double the rates for non-Indians. Age-adjusted mortality rates for acute rheumatic fever were low and showed no consistent trends between the sexes and among the various ethnic groups (Table 2).

Age-specific mortality rates for chronic rheumatic heart disease generally decreased among Hispanics and non-Hispanic whites in each age group during the study period (Figures 1 through 4); between 1968 and 1977, however, American Indians showed age-specific increases in many age groups (Table 4). These increases were greatest among American Indian men aged 55 to 74 years and among American Indian women aged 65 to 74 years (Table 4).

TABLE 1.—*Population Estimates for New Mexico Residents, 1960, 1970, and 1980**

Ethnic Group	*1960*	*1970*	*1980*
Hispanic			
Male	166,652	192,967	233,315
Female	173,805	197,721	238,677
American Indian			
Male	27,586	35,035	51,032
Female	28,669	37,753	55,087
Non-Hispanic white			
Male	275,700	259,153	341,328
Female	259,606	265,974	350,733

*Based on United States Census Bureau figures.

TABLE 2.—*Age-Adjusted* Annual Mortality Rates From Acute Rheumatic Fever in New Mexico, 1958-1982 (per 100,000)*

	5-Year Time Period				
Ethnic Group by Sex	*1958-1962*	*1963-1967*	*1968-1972*	*1973-1977*	*1978-1982*
Male					
Non-Hispanic white, n=24†	0.3	0.2	0.5	0.3	0.2
Hispanic, n=13	0.2	0.1	0.1	0.6	0.4
American Indian, n=5	0.6	1.0	0.0	1.3	0.2
US whites‡	0.4	0.3	0.1	0.1	0.05
Female					
Non-Hispanic white, n=39	0.4	0.1	0.4	0.6	0.7
Hispanic, n=22	0.4	0.3	0.4	0.4	1.0
American Indian, n=5	1.9	0.4	0.9	0.0	0.7
US whites‡	0.4	0.2	0.1	0.04	0.03

*Adjusted to 1970 United States population.
†Number of deaths during 25-year period.
‡Rates calculated for mid-point of each 5-year interval.

TABLE 3.—*Age-Adjusted* Annual Mortality Rates From Chronic Rheumatic Heart Disease in New Mexico, 1958-1982 (per 100,000)*

	5-Year Time Period				
Ethnic Group by Sex	*1958-1962*	*1963-1967*	*1968-1972*	*1973-1977*	*1978-1982*
Male					
Non-Hispanic white, n=407†	10.5	7.1	7.2	4.5	3.0
Hispanic, n=230	9.7	9.9	5.6	6.5	3.6
American Indian, n=55	10.2	6.3	14.9	10.0	1.4
US whites‡	10.1	7.4	7.4	5.8	2.5
Female					
Non-Hispanic white, n=477	10.6	8.5	5.7	4.0	3.2
Hispanic, n=296	16.4	11.3	7.2	4.4	3.4
American Indian, n=52	6.6	7.8	10.6	8.5	4.7
US whites‡	10.3	9.8	7.1	5.8	3.7

*Adjusted to 1970 United States population.
†Number of deaths during 25-year period.
‡Rates calculated for mid-point of each 5-year interval.

Discussion

The dramatic decrease in the incidence of acute rheumatic fever in various communities in the United States has been well described. Since 1940 when an estimated 250,000 new cases occurred,[1] acute rheumatic fever has become a rare disease. During the 1960s, high rates of acute rheumatic fever occurred in Baltimore,[11] Nashville,[10] and New York City.[12] During the subsequent decades, incidence rates for acute rheumatic fever declined in Baltimore,[1,28] with comparably low rates reported from Memphis, Tennessee[29]; Rhode Island[30]; Fairfax County, Virginia[31]; and suburban Los Angeles.[32] Population-based surveys in Rochester, Minnesota, show that incidence rates of acute rheumatic fever decreased annually from 13.6 per 100,000 population in 1935 to 1949 to 2.7 per 100,000 population in 1965 to 1978.[2] Thus, despite recent reports of isolated epidemics of acute rheumatic fever,[33-37] most national data clearly indicate falling trends in disease incidence.

Nationwide declines in mortality rates for acute rheumatic fever and for chronic rheumatic heart disease have paralleled their declining incidence.[4] From 1919 to 1961, the national mortality rate for acute rheumatic fever fell from 3.0 per 100,000 population to 0.4 per 100,000 population,[38] and current mortality rates for acute rheumatic fever approximate 0.1 per 100,000 population.[4] The nationwide mortality rate for chronic rheumatic heart disease fell from 20.2 per 100,000 population in 1939 to 2.2 per 100,000 population in 1982 (Table 3).[2] In New Mexico, mortality rates for acute rheumatic fever and chronic rheumatic heart disease have been declining since the 1930s. New Mexico's mortality rate for chronic rheumatic heart disease has remained slightly below national rates since the 1930s,[38] but the annual mortality rate for acute rheumatic fever in New Mexico has exceeded the national rate in certain years.

The few published studies that have examined racial or ethnic effects on the occurrence of acute rheumatic fever have documented substantial racial differences.[3,7-12,27,39] Among school children aged 5 to 9 years in Baltimore, black children had a rate of acute rheumatic fever nearly three times that of white children during the years 1960 to 1964,[11] and a rate nearly twice that of whites for children aged 5 to 14 years during a survey carried out in 1968.[28] Comparable racial differences were noted in Nashville from 1963 to 1969.[10] In Manhattan, Puerto Rican children aged 5 to 14 years had incidence rates of acute rheumatic fever from 1963 to 1965 that were triple the rates for inner-city white children

TABLE 4.—*Age-Specific Mortality Rates From Chronic Rheumatic Heart Disease in American Indians in New Mexico, 1958-1982 (per 100,000)*

		5-Year Time Period				
Age Group, yr	*Sex*	*1958-1962*	*1963-1967*	*1968-1972*	*1973-1977*	*1978-1982*
35-44	♂	0.0	12.3	30.3	5.3	0.0
	♀	0.0	5.2	5.1	0.0	3.7
45-54	♂	20.2	0.0	8.7	15.3	0.0
	♀	19.7	15.4	38.2	19.9	10.8
55-64	♂	14.1	12.2	35.6	21.1	9.3
	♀	14.0	22.0	10.8	38.1	16.2
65-74	♂	41.7	17.4	68.1	60.0	0.0
	♀	0.0	34.5	52.4	44.7	11.6
75+	♂	37.3	30.3	29.7	0.0	0.0
	♀	0.0	0.0	0.0	0.0	0.0

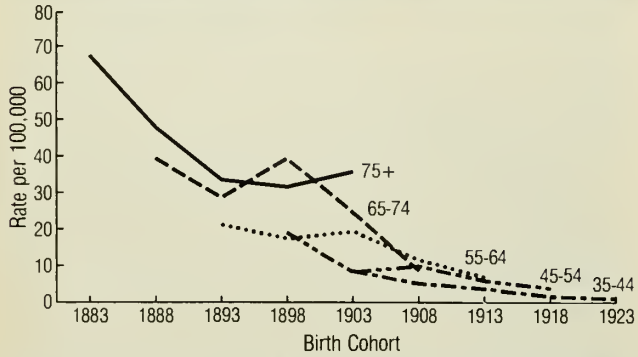

Figure 1.—The graph shows the chronic rheumatic heart disease mortality in non-Hispanic white men by age group and birth cohort (rates per 100,000).

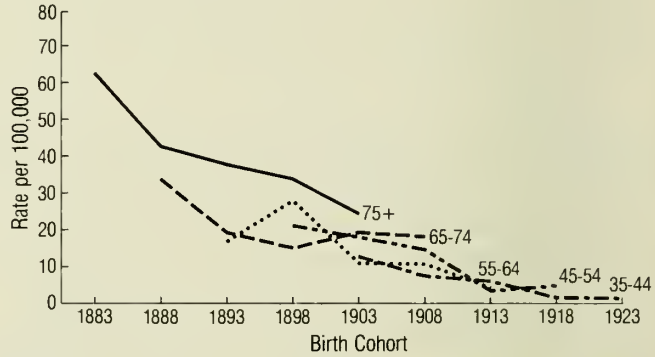

Figure 2.—The graph shows the chronic rheumatic heart disease mortality in non-Hispanic white women by age group and birth cohort (rates per 100,000).

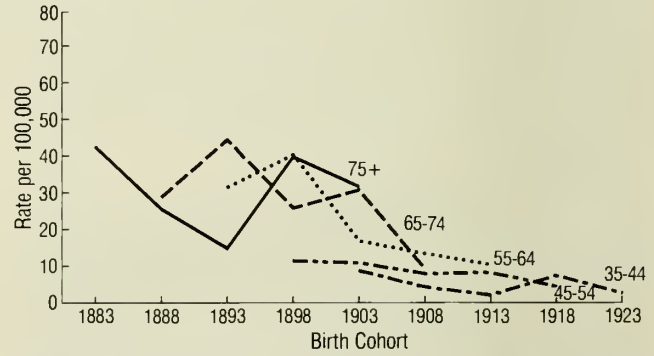

Figure 3.—The graph shows the chronic rheumatic heart disease mortality in Hispanic men by age group and birth cohort (rates per 100,000).

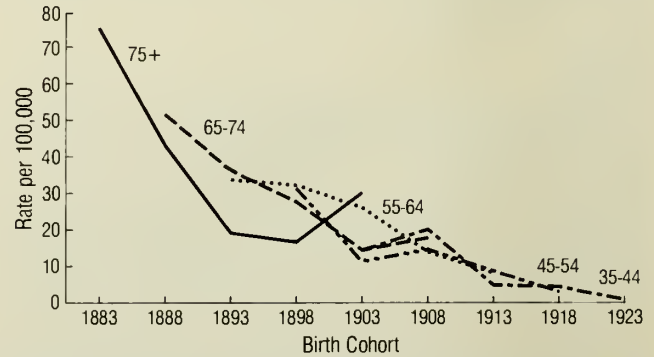

Figure 4.—The graph shows the chronic rheumatic heart disease mortality in Hispanic women by age group and birth cohort (rates per 100,000).

of similar age (78 per 100,000 versus 23 per 100,000).[12] Samoan children in Hawaii had high rates of acute rheumatic fever in a 1976 to 1980 survey (96.5 cases per 100,000) when compared with native Hawaiians (27.2 per 100,000), whites (9.0 per 100,000), and Japanese (0 cases per 100,000).[8] The incidence rate of acute rheumatic fever for Navajo children, aged 5 to 14 years, during the period 1962 through 1977 was 18.8 per 100,000.[7] Hispanic and black children in a Los Angeles suburb had a rate of hospital admissions for acute rheumatic fever five times higher than that for non-Hispanic whites, although the overall rate in the San Fernando Valley study area was low (0.21 per 100,000 population).[32] Hispanic school children in Denver also had rates of rheumatic heart disease and histories of acute rheumatic fever that exceeded non-Hispanic white rates.[40] In New Mexico, however, we observed no consistent excesses in age-adjusted mortality rates from acute rheumatic fever in Hispanics or American Indians when compared with rates for non-Hispanic whites (Table 2).

Among Hispanics and non-Hispanic whites, our data show clear trends, in parallel with national trends, toward decreasing mortality rates from chronic rheumatic heart disease (Table 3). This decrease may reflect improvements in diagnosis, improved access to medical care, an increased awareness of the importance of treating streptococcal pharyngitis, an increasing number of persons undergoing heart valve replacements, and a growing recognition of the need for antibiotic prophylaxis in patients with chronic rheumatic heart disease.[1,3,5,6,41] Changing host susceptibility and changes in the etiologic agent, the *Streptococcus,* have also been postulated as important factors in the decline in incidence and mortality from streptococcal disease.[1,5]

American Indians in New Mexico are the least economically advantaged group in the state. In other studies, lower economic status has been associated with higher mortality rates for acute rheumatic fever and chronic rheumatic heart disease[38,39]; no consistent patterns emerge, however, from a comparison of New Mexico's acute rheumatic fever mortality rates for American Indians with those of the other ethnic groups over all time periods. Nonetheless, age-adjusted mortality rates for chronic rheumatic heart disease in American Indians were double those rates in non-Indians for 1968 to 1977 and were notably elevated in older American Indians. The biggest decrease in mortality from acute rheumatic fever and chronic rheumatic heart disease in this ethnic group occurred in the most recent time period, 1978 to 1982. Although no published data explain this recent decline for all of New Mexico's American Indians, the increasing use of antibiotic prophylaxis for streptococcal infections among Navajo patients with rheumatic heart disease may have contributed to the decline in mortality rates.[12]

Our study has limitations that must be considered. Detecting all cases of acute rheumatic fever and chronic rheumatic heart disease is difficult because the diagnoses are based on clinical criteria, and it is probable that only cases under medical care were recorded on the death certificate as having died of these causes. The validity of death certificate cause-of-death statements for numerous diseases has been well described[42-44] and need not be discussed in detail here. In New Mexico, however, additional bias in death certificate-based studies may be related to ethnic group: a larger proportion of death certificates was coded into the category "symptoms, senility, and ill-defined conditions" for American Indians than for Hispanics and non-Hispanic whites.[15] Thus, misclassification of acute rheumatic fever- and chronic rheumatic heart disease-related deaths may be greater among American Indians than among non-Indians. Our rate calculations based on ethnic identification may also be subject to bias. For Hispanics in New Mexico, however, we found a high level of concordance (greater than 96%) between self-reported Hispanic ethnicity among subjects who participated in a statewide case-control lung cancer study conducted from 1980 through 1982[45] and the code assigned by the Bureau of Vital Statistics to deceased subjects.[25] This observation suggests that a misclassification of Hispanics was not a major source of bias in the study. Although we have not carried out comparable validation studies of American Indians in this state, determining the ethnicity of American Indians in New Mexico is less problematic than determining Hispanic ethnicity. Changes in coding schemes beginning in the eighth revision of the International Classification of Diseases resulted in a larger number of cardiac deaths classified as rheumatic in etiology; this change in coding could add additional bias to our results.[46] In addition, census undercounts of American Indians and instability of mortality rates due to a small number of deaths from acute rheumatic fever and chronic rheumatic heart disease limit our ability to detect trends and ethnic differences in mortality.

Despite the limitations of our study, we have shown changing patterns of mortality from acute rheumatic fever and chronic rheumatic heart disease in New Mexico from 1958 to 1982. We have also shown that ethnicity influenced chronic rheumatic heart disease mortality risk in this state. Although American Indians showed much higher mortality rates for chronic rheumatic heart disease than did non-Indians from 1968 to 1977, the overall trends of decreasing rheumatic heart disease mortality in New Mexico were similar to national trends from the late 1950s through the early 1980s.

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Precautions on Rifampin

PLEASE TELL PATIENTS receiving rifampin a few things: First, if a patient is pregnant, tell her to not take it, because there is concern about it being a teratogenic agent. Second, if a woman is on birth control pills, tell her that rifampin inactivates the effect of birth control pills. Third, if patients wear contact lenses, tell them that rifampin is excreted in the tears, and it will stain their contact lenses. And, fourth, my favorite, tell them that it will turn their urine orange—and I mean really orange.

—CHARLES SHABINO, MD

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Clinical Review

Laboratory Evaluation of a Bleeding Patient

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Most causes of abnormal bleeding can be determined from a complete blood count including platelet count and bleeding, prothrombin, activated partial thromboplastin, and thrombin times. Occasionally, further evaluation is necessary, such as tests of factor XIII function, fibrinolysis, and vascular integrity. Possible diagnoses include disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, vitamin K deficiency, von Willebrand's disease, heparin-induced thrombocytopenia, acquired inhibitors of factor VIII, lupus anticoagulants, and coagulation disorders related to the acquired immunodeficiency syndrome.

(Wallerstein RO Jr: Laboratory evaluation of a bleeding patient. West J Med 1989 Jan; 150:51-58)

The cause of abnormal bleeding frequently can be determined from the history alone, which is then supplemented by laboratory testing. A systematic approach to the laboratory evaluation of a bleeding patient permits a quick and precise identification of the problem and the specific therapy to be chosen, thus avoiding the unnecessary delay, expense, and risk of "shotgun therapy." In addition to quickly identifying the common causes of bleeding, such a system should also identify the uncommon causes of abnormal bleeding. This review provides clinicians with one such systematic approach. Several textbooks offer similar approaches and further discussion for interested readers.[1-6]

To interpret the laboratory results intelligently, the pretest probability for particular abnormalities must first be established. From the history, it is determined whether the bleeding problem is congenital or acquired. Congenital bleeding disorders are suggested by a family history of abnormal bleeding or a personal history of bleeding from the umbilical stump, bleeding at the time of circumcision, bleeding for more than 24 hours or late rebleeding following a tooth extraction, recurrent epistaxis requiring packing or cautery, or excessive bleeding requiring transfusion following simple surgical procedures, such as tonsillectomy. Occasionally, however, congenital bleeding disorders, particularly if mild, may not present until adulthood at the time of major surgical procedures or comorbid conditions. A careful physical examination establishes whether bleeding is localized or systemic. In addition, it is often useful to consider whether the bleeding is "platelet-type bleeding," which is characterized by bleeding at mucocutaneous surfaces (epistaxis, menorrhagia, hematuria, gastrointestinal bleeding, or superficial bruising and petechiae), or coagulation factor deficiency-type bleeding, which is classically characterized as "deep bleeding" (such as into joints or muscles). Both types of bleeding produce cutaneous ecchymoses, although with platelet-type bleeding the ecchymoses are superficial and with coagulation factor-type bleeding, deep bleeding often forms a palpable mass in the center of the ecchymosis. In addition, platelet-type bleeding often begins immediately with the interruption of capillaries, whereas coagulation factor deficiency-type bleeding will be delayed. Finally, particularly in evaluating postoperative bleeding, it must be determined whether the bleeding is occurring only within the operative field and therefore could be due to a surgical problem or whether the bleeding is generalized—that is, oozing around intravenous catheters or arterial lines.

A careful review of the patient's prescribed and nonprescribed medications is essential. The use of broad-spectrum antibiotics combined with poor nutrition can result in vitamin K deficiency. A history of aspirin and nonsteroidal anti-inflammatory drug use may unmask a qualitative platelet defect or von Willebrand's disease. Many drugs can produce thrombocytopenia. Finally, there are rare idiosyncratic abnormalities of coagulation—such as isoniazid-induced inhibition of factor XIII action[7]—that can be drug-related.

From specific aspects of the history, physical examination, and a careful review of the medications the patient is currently receiving and has recently received, a preliminary estimate can be made of the probable cause of the bleeding.

In virtually all patients who are hemorrhaging, a thrombin time, prothrombin time, activated partial thromboplastin time, complete blood count including a platelet count and a peripheral smear for review, and a bleeding time should be done. These initial screening studies should identify most causes of abnormal bleeding, with a few exceptions that will be discussed later.

As shown in Figure 1, the thrombin, prothrombin, and partial thromboplastin times measure different aspects of the coagulation cascade. For all three measurements, however, the final endpoint is the formation of fibrin strands determined mechanically or by a decreased transmission of light.

Thrombin Time

The first test results to be looked at should be of the thrombin time. The thrombin time is done by adding a diluted solution of the enzyme thrombin to a citrated specimen of the patient's plasma, and the time required to convert fibrinogen to fibrin polymer is measured. The thrombin time may be prolonged by a decreased amount of dysfunctional fibrinogen or by substances that interfere with fibrin polymerization

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Reprints are not available.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CBC = complete blood count
DIC = disseminated intravascular coagulation
FDP = fibrin degradation products
PTT = partial thromboplastin time
TPA = tissue plasminogen activator

(Table 1). One of the most common problems, particularly in the intensive care unit, is contamination of the blood specimen by heparin when the specimen is drawn through an arterial line. Therefore, specimens for coagulation studies should always be drawn through a separate percutaneous venipuncture. If heparin contamination may be the cause of a prolonged thrombin time, a reptilase time—reptilase being another thrombinlike enzyme that is not inactivated by heparin—can be done or the heparin can be inactivated or removed in vitro before the thrombin time is determined by adding protamine, heparin neutralizer powder (Heparsorb; Organon Teknika), or toluidine blue.

A long thrombin time not due to heparin contamination in a patient with generalized bleeding is highly suggestive of disseminated intravascular coagulation (DIC). No one test is totally sensitive or specific for the diagnosis of DIC.[8-10] In most hospitals, fibrin degradation or "split" products (FDPs), fibrinogen, and a fibrin monomer are measured. Plasmin degrades both fibrinogen and fibrin to form fragments X, Y, D, and E, which are commonly measured in a

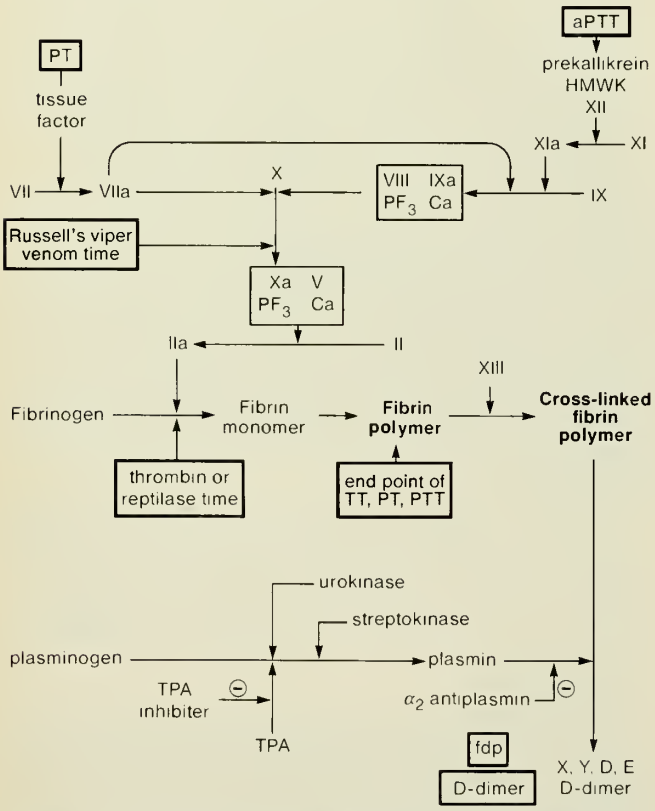

Figure 1.—The sequence of coagulation and fibrinolytic reactions is shown, with roman numerals indicating coagulation factors. Boxes indicate sites of initiation and termination of coagulation studies and of sampling of fibrinolytic products. aPTT = activated partial thromboplastin time, Ca = calcium, fdp = fibrinogen degradation product, HMWK = high-molecular-weight kininogen, PF_3 = platelet factor 3, PT = prothrombin time, PTT = partial thromboplastin time, TPA = tissue plasminogen activator, TT = thrombin time

TABLE 1.—*Etiology of a Prolonged Thrombin Time*

Heparin administration or contamination
Fibrin split products
Hypofibrinogenemia
Dysfibrinogenemia
Inhibitor of fibrin polymerization
  Paraprotein in myeloma or Waldenström's macroglobulinemia
  Heparinoid or heparinlike inhibitor
  Antibody to thrombin
Hyperfibrinogenemia—does not produce clinical bleeding

serum specimen by their ability to agglutinate latex beads coated with antibody to fragments D and E. Theoretically all of the fibrinogen is removed when the plasma is converted to serum by clotting, but incomplete defibrinogenation due to heparin or dysfibrinogenesis is one cause of a false-positive FDP test. A rheumatoid factor may also cause a false-positive test by cross-linking the antibody-coated latex beads. A new test for the proteolytic products of plasmin cleavage of fibrin polymer called the D-dimer test uses a monoclonal antibody to an antigen present only on factor XIII cross-linked fibrin polymer and appears in early testing to be a rapid, sensitive, and theoretically more specific means for measuring FDP levels.[11] Neither test is specific for DIC, however; they simply indicate the presence of fibrinolysis, whether abnormal or physiologic. FDP levels are commonly mildly elevated in postoperative patients—FDP 10 to 40 μg per ml or D-dimer 2 to 8 μg per ml. High levels, however—FDP > 40 μg per ml or D-dimer > 8 μg per ml—are suggestive of DIC. FDP levels as determined by the standard test are elevated in cases of renal and hepatic dysfunction due to delayed clearance. The specificity of the D-dimer test in such cases is still unclear.

Evidence of fibrinolysis by elevated FDP or D-dimer levels only is not specific for DIC, but documenting simultaneous ongoing thrombin action by finding elevated levels of circulating fibrin monomer strongly suggests DIC. Fibrin monomer is formed after fibrinopeptides A and B are cleaved from fibrinogen by thrombin. When fibrin monomer is present in low concentrations by itself or in higher concentrations with FDPs, which interfere with monomer polymerization, adding protamine sulfate can permit the monomer to polymerize. This is the basis for the protamine paracoagulation test.[12] If properly done, a strongly positive test is less sensitive for DIC than measuring FDP levels but is more specific and, in a patient in whom DIC is suspected, constitutes strong supportive evidence. A microangiopathic peripheral smear with fragmented erythrocytes is neither sensitive nor specific for DIC but, when present, supports the diagnosis.

The plasma fibrinogen concentration is usually determined by adding concentrated thrombin and measuring the total clottable protein. A low fibrinogen determination may be due to either congenital afibrinogenemia or acquired hypofibrinogenemia, which is most commonly due to DIC. The other possibility, however, would be a dysfibrinogenemia, which may be congenital or acquired. As mentioned, heparin administration or contamination will prolong the thrombin time but not the reptilase time. In a patient not receiving heparin, discordance between the thrombin and reptilase times suggests the possibility of a dysfibrinogenemia with alteration of one but not both cleavage sites. Often, however, both times are prolonged and an immuno-

logic determination of fibrinogen must be done. If by adding thrombin a functional fibrinogen concentration is found that is less than 50% of the immunologic fibrinogen, this strongly suggests dysfibrinogenemia. Most of the cases of congenital dysfibrinogenemia reported to date have been autosomal dominant, and family studies are helpful. Acquired dysfibrinogenemia has most often been reported in patients with severe liver dysfunction or hepatoma.

In summary, a long thrombin time not due to heparin in a patient with generalized bleeding is highly suggestive of DIC. A low or falling fibrinogen level, high levels of FDP or D-dimer, a strongly positive protamine sulfate paracoagulation test, a low or falling platelet count, and a microangiopathic smear would be diagnostic of DIC. In practice combinations of these must be used to make the diagnosis. Because platelets and fibrinogen are acute-phase reactants and their levels may be elevated in pregnant women and cases of infection, a single normal level of these does not rule out DIC. In these circumstances, a repeat "DIC screen" in a few hours may reveal a falling platelet count and fibrinogen level consistent with active DIC.

In patients with multiple myeloma or Waldenström's macroglobulinemia, paraproteins that inhibit the polymerization of fibrin monomer may also prolong the thrombin time and produce clinical bleeding. These paraproteins may also interfere with platelet function.

A few cases have been reported of patients with heparin-like or "heparinoid" inhibitors who have laboratory features suggesting heparin effect—long thrombin time, normal reptilase time, or correction of thrombin time by protamine, toluidine blue, or heparinase—but who had not received heparin and in whom the electrophoretic mobility of the inhibitor was distinct from that caused by heparin.[13]

A few patients have been seen, all with prosthetic heart valves, in whom antibodies to thrombin have developed that could be shown by a long thrombin time uncorrected by adding normal plasma, a normal reptilase time, and antibody binding to thrombin in vitro (Ray Stricker, MD, Assistant Professor of Medicine, University of California, San Francisco, oral communication, July 1987).

It has recently been shown that hyperfibrinogenemia—>100 mg per dl above normal—can prolong the thrombin time but does not cause abnormal bleeding.[14]

Prothrombin Time

If the thrombin time is normal, the prothrombin and partial thromboplastin times are then evaluated. If the thrombin time is normal, the prothrombin time long, and the partial thromboplastin time (PTT) normal, then the patient has either mild liver disease, early vitamin K deficiency, anticoagulation with sodium warfarin therapy, or the relatively rare factor VII deficiency. The prothrombin time, which is determined by adding calcium and tissue thromboplastin to a specimen of the patient's platelet-poor citrated plasma, is sensitive to factor VII. Of the vitamin K-dependent clotting factors, factor VII has the shortest half-life, which is about six hours. Therefore, with active vitamin K depletion by decreased intake, poor gastrointestinal absorption, or warfarin ingestion, the prothrombin time will prolong before the PTT will. In fact, whenever a patient has prolongation of both the prothrombin time and the PTT, but the prothrombin time seems prolonged in relation to the PTT, vitamin K deficiency, warfarin therapy, or liver disease should be considered.

Vitamin K is derived either from diet (vitamin K_1) or from synthesis by intestinal bacteria (vitamin K_2). Both require bile acids and adequate mucosal function for absorption. The possibility of vitamin K deficiency must always be considered in a patient with a normal thrombin time but prolonged prothrombin and partial thromboplastin times, particularly if the patient is poorly nourished and on broad-spectrum antibiotic therapy. Furthermore, cephalosporin antibiotics with a methylthiotetrazole ring may actually inhibit vitamin K-dependent carboxylation, and clinical bleeding with a long prothrombin time may require the administration of fresh frozen plasma because the defect may not be corrected for 24 to 36 hours after treatment with vitamin K.[15]

If a normal thrombin time and both a long prothrombin time and PTT are found, causes to be considered are severe liver disease, severe vitamin K deficiency, warfarin therapy, massive transfusion of packed cells without fresh frozen plasma, the use of plasmanate or a replacement source of inactivated clotting factor other than fresh frozen plasma, or one of the rare deficiencies of the common pathway (Table 2). Congenital deficiencies of factors II, V, or X are rare.[16] A deficiency of factor X can occur in patients with amyloidosis; usually there is hepatosplenomegaly, and factor X replacement with fresh frozen plasma may be unsuccessful because of an apparent accelerated clearance of factor X due to binding to the amyloid protein.[17] Acquired factor II deficiency or hypoprothrombinemia may sometimes be seen in association with a lupus anticoagulant. It has also been reported following a massive aspirin overdose. Acquired anti-

TABLE 2.—*Etiology of a Normal Thrombin Time but Prolonged Prothrombin and Partial Thromboplastin Times*

- Vitamin K deficiency
- Sodium warfarin administration
- Moderate to severe liver disease
- Coagulation factor washout
  - Massive transfusion (>10 units in 24 hours)
  - Plasmapheresis without fresh frozen plasma replacement
- Common pathway deficiency
  - Congenital deficiency of factor II, factor V, or factor X
  - Acquired factor X deficiency due to amyloid
  - Acquired factor II deficiency in association with lupus anticoagulant or massive aspirin overdose
  - Acquired antibody to factor V

TABLE 3.—*Etiology of Isolated Prolongation of Partial Thromboplastin Time*

- Mixing study corrects
  - Bleeding disorder
    - Factor VIII deficiency—hemophilia A or von Willebrand's disease
    - Factor IX deficiency—hemophilia B
    - Factor XI deficiency
  - No bleeding disorder
    - Deficiency of factor XII, prekallikrein, or high-molecular-weight kininogen
- Mixing study does not correct or prolongs with 1- to 4-hour incubation
  - Bleeding disorder—check factors VIII, IX, and XI
    - Acquired inhibitor of factor VIII
  - No bleeding disorder
    - Lupus anticoagulant—check diluted Russell's viper venom test

bodies to factor V are rare and have occurred postoperatively, possibly related to the use of streptomycin.[18] Finally, the patient may have congenital deficiency of the vitamin K-dependent γ-carboxylation enzyme. Such patients have defective synthesis of γ-carboxylated II, VII, IX, and X and appear to have vitamin K deficiency but have adequate vitamin K stores.[19]

Partial Thromboplastin Time

If there is an isolated prolongation of the partial thromboplastin time, the diagnostic approach should be as shown in Table 3. Isolated prolongation of the PTT represents either a deficiency or an inhibition of the intrinsic clotting pathway. It is absolutely critical that these two causes be differentiated because the treatments are entirely different. Therefore, the first test to be done after identifying an isolated, long PTT is a mixing study (also called an inhibitor screen).

The mixing study makes use of the fact that the activated PTT will prolong only when the level of any of the factors is below 25% to 40%. Therefore, if one part of the patient's plasma is mixed with one part of normal control plasma, even if the patient's plasma has absolutely no factor activity, the PTT will be corrected because 50% of the test mixture is "normal." If this mixing study does not result in full correction of the PTT, it can be concluded that an inhibitor is present that is interfering not only with the patient's plasma but with the added normal plasma as well. Although mixing studies are most commonly applied in evaluating a long PTT, the same principles of using a 1:1 mixture to differentiate a factor deficiency from an inhibitor apply to the thrombin time, prothrombin time, and other coagulation studies as well. In clinical practice, the most common types of inhibitors that prolong the PTT are an acquired inhibitor to factor VIII and a lupus anticoagulant.

Acquired inhibitors to factor VIII occur in 5% to 20% of patients with severe (less than 1% factor VIII activity) hemophilia A, generally before the age of 10. Factor IX inhibitors in patients with hemophilia B are less common. There are also spontaneously occurring inhibitors to factor VIII in persons without hemophilia. These may occur postpartum, as a complication of immunologic and autoimmune disorders, in malignant hematologic disorders, in drug reactions particularly to penicillin, and in elderly patients for no apparent reason. One interesting characteristic of acquired factor VIII inhibitors is that the bleeding tends to be out of proportion to the prolongation of the PTT. When doing a mixing study, PTTs should always be measured not only at time zero, but also on mixes incubated for one, two, and four hours or even overnight to detect antibodies of low amplitude or low affinity, which may still cause severe clinical bleeding. Clinicians must be aware of the existence of and methods of diagnosing acquired factor VIII inhibitors because specific therapeutic approaches are indicated. These include plasmapheresis, immunosuppressive therapy, and the use of an anti-inhibitor coagulant complex.[20]

Lupus anticoagulants occur in 6% to 25% of patients with systemic lupus erythematosus,[21] but they may also occur in cases of drug abuse, hematologic malignancy, or in patients with the acquired immunodeficiency syndrome (AIDS).[22] Finally, the lupus anticoagulant has been recognized as a cause of recurrent spontaneous abortion and second- and third-trimester fetal death.[23] Because corticosteroid therapy appears to suppress the lupus anticoagulant and permit successful delivery in many although not all of these cases, screening of women who have recurrent abortions using an activated PTT or diluted Russell's viper venom may be indicated.

Lupus anticoagulants are antibodies that bind to and inactivate the phospholipid component of the reagents in the activated PTT. Characteristically, when a mixing study is done, the 50-50 mixture will be uncorrected at time zero. In general, a mixing study that partially corrects at time zero and then prolongs with timed incubation suggests an acquired inhibitor to factor VIII. On the other hand, minimal correction at time zero suggests a lupus anticoagulant. Other tests that may be useful in evaluating a suspected lupus anticoagulant include a diluted Russell's viper venom test,[24] a tissue thromboplastin inhibition test, platelet neutralization test, and an anticardiolipin antibody test.

Lupus anticoagulants alone, however, are not a cause of abnormal bleeding and actually predispose patients to thrombosis. But they can be associated with acquired hypoprothrombinemia, which would be suggested by a significant prothrombin time as well as PTT prolongation. This is due to a nonneutralizing antibody to prothrombin that causes accelerated clearance of the antibody-prothrombin complex. Because the antibody is nonneutralizing, it does not inactivate the prothrombin, so in vitro a mixing study on the long prothrombin time would correct, but in vivo prothrombin would undergo accelerated clearance. Thus, although lupus anticoagulants are not generally associated with bleeding, if a prothrombin time is significantly prolonged—more than 1.5 times control—a specific factor II level should be measured.[25]

When evaluating isolated prolongation of the PTT, if the mixing study fully corrects and stays corrected with incubation, then a deficiency of one of the intrinsic pathway factors is present. Only deficiencies of factors VIII, IX, and XI cause clinical bleeding. Deficiencies of factor XII, prekallikrein, and high-molecular-weight kininogen do not cause bleeding disorders. A factor VIII level should be checked, then a factor IX level, and then a factor XI level; this is the order of their frequency of incidence. If there is a low factor VIII level, it may be due to either congenital factor VIII deficiency—hemophilia A—or von Willebrand's disease. A diagnosis of von Willebrand's disease would be suggested by the finding of a prolonged bleeding time as well as a prolonged PTT and would be confirmed by studies that will be discussed.

Von Willebrand's protein levels can fluctuate, but a patient who has bleeding due to von Willebrand's disease will always have a long bleeding time. Because von Willebrand's protein levels increase with pregnancy or estrogen administration, the absence of bleeding with deliveries or even cesarean section does not rule out von Willebrand's disease.

Platelet Count

In a patient with abnormal bleeding, if the thrombin time, prothrombin time, and PTT are normal, the probability of a coagulation factor problem involving the intrinsic, extrinsic, or common pathway is less than 1%.[26] The platelet count should next be evaluated. There is in general a linear relationship between the platelet count and the bleeding time, with the bleeding time prolonging progressively as the platelet count falls below 100,000 per μl down to a platelet count of 10,000 per μl below which the bleeding time is

greater than 30 minutes. This linear relationship between 10,000 and 100,000 per μl is expressed as

bleeding time (minutes) = 30.5 − platelet count ÷ 3,850

using a standard modified template bleeding time.[27] Patients with platelet counts between 50,000 and 100,000 per μl are unlikely to hemorrhage except with major trauma or an operation. Patients with platelet counts between 20,000 and 50,000 per μl are unlikely to have spontaneous bleeding. If the bleeding time is out of proportion to the thrombocytopenia or if there is spontaneous bleeding with greater than 20,000 platelets per μl, a qualitative platelet defect, such as uremia or the use of a nonsteroidal anti-inflammatory agent, may be the cause.

In further evaluating a patient with abnormal bleeding and thrombocytopenia, the results of a complete blood count (CBC) should be looked at to determine whether this is an isolated thrombocytopenia or if there is also anemia or leukopenia. Thrombocytopenia with pancytopenia is likely to represent a primary bone marrow disorder like acute leukemia, aplastic anemia, or myelodysplasia. With a finding of thrombocytopenia and anemia, the peripheral blood smear should be carefully examined for any evidence of red cell fragmentation—microangiopathy—that would indicate one of the disorders listed in Table 4. Thrombocytopenia due to DIC would be unlikely with a normal thrombin time, prothrombin time, and PTT when DIC is due to sepsis or an obstetric complication. With "compensated" or "low-grade" DIC in patients with malignancy, however, it is not uncommon to have only minimal or no prolongation of the prothrombin time and PTT. In fact, on occasion there may be actual shortening of the PTT because of activated clotting factors already present in the test tube before the phospholipid and kaolin are added. Elevated levels of fibrin split products or D-dimer should always be present in these patients, however, and often there is microangiopathy on the peripheral smear or a strongly positive protamine sulfate test.

Because of dramatic advances in the therapy for thrombotic thrombocytopenic purpura in the past decade, clinicians must be aware of the clinical presentation and diagnosis of this syndrome.[28,29] Patients with this disorder present with thrombocytopenia, a microangiopathic hemolytic anemia with high lactic dehydrogenase levels, fever, mild renal abnormalities such as microscopic hematuria, and neurologic disturbances. The neurologic disorders may occur as headache, an altered mental state, focal neurologic deficits, seizures, and coma. Untreated, the mortality may be as high as 95%. Plasmapheresis with fresh frozen plasma yields complete response rates of 70%. If plasmapheresis fails to elicit a response, splenectomy and administering dextran and steroids may be effective.[30] Therefore, in a bleeding patient with thrombocytopenia and anemia, a careful review of the peripheral smear and consideration of thrombotic thrombocytopenic purpura are imperative.

The hemolytic-uremic syndrome in adults appears to share many pathophysiologic features with thrombotic thrombocytopenic purpura but has more impressive renal findings (overt uremia) and less impressive neurologic findings, and it seems to respond less well to plasmapheresis.

If the findings of a CBC aside from thrombocytopenia are normal and the peripheral smear is normal, the medication regimen the patient has been on should be carefully evaluated. Many drugs have been reported to cause immune thrombocytopenia, but a few do so with increased frequency (Table 5).

Heparin-induced thrombocytopenia deserves particular emphasis.[31] It occurs in 1% to 10% of treated patients, depending on the source of the heparin. It usually occurs five to ten days after starting the heparin therapy but may be seen earlier in patients previously treated with heparin. In a small subset of these patients, acute arterial and venous thrombosis explosively develop with the occurrence of thrombocytopenia. This catastrophic event has a high morbidity and mortality. "Recurrent" thrombosis or embolization in a patient on heparin therapy must always raise the possibility of heparin-induced thrombocytopenia because failure to stop the therapy is likely to be fatal. Serotonin release from normal platelets incubated with a specimen of the patient's plasma plus heparin has been proposed as a test for heparin-induced thrombocytopenia,[32] but this procedure is not widely available. The treatment of heparin-induced thrombocytopenia with and without thrombosis is controversial.[33]

In most cases, patients with bleeding and a platelet count of less than 10,000 per μl with normal results on a CBC will have idiopathic thrombocytopenic purpura. Generally a bone marrow aspirate and biopsy should be done to ensure an adequate number of megakaryocytes and to rule out primary bone marrow disorders. An antiplatelet antibody test is generally sensitive although not entirely specific for idiopathic thrombocytopenic purpura. Isolated thrombocytopenia may be the first sign of AIDS, and a test for antibodies to the human immunodeficiency virus should be considered when thrombocytopenia occurs in patients at risk.[34]

TABLE 4.—*Disorders That Cause Thrombocytopenia With Anemia and Microangiopathy on a Peripheral Blood Smear*

Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Hemolytic-uremic syndrome
Malignant hypertension
Eclampsia
Vasculitis
Dysfunctional prosthetic valve
Widespread metastatic cancer
Leaking aortic aneurysm

TABLE 5.—*Common Drugs That Cause Thrombocytopenia*

Quinidine sulfate, gluconate, or polygalacturonate
Quinine sulfate or dihydrochloride
Sulfonamides
Trimethoprim and sulfamethoxazole
Heparin
Gold sodium thiomalate
Thiazides
Alcohol
Chemotherapeutic agents

Bleeding Time

If the thrombin time, prothrombin time, PTT, and platelet count are all normal, the bleeding time should next be evaluated. As mentioned, there is generally a linear correlation between the platelet count and the bleeding time below a platelet count of 100,000 per μl. Below a platelet count of 10,000 per μl, the linear relationship is lost and it is unnecessary and inappropriate to do a bleeding time. With a platelet

count between 10,000 and 100,000 per μl in a patient who is bleeding, however, such a test is appropriate because if the bleeding time is found to be out of proportion to the platelet count, it suggests there is a qualitative as well as quantitative platelet disorder.

The differential diagnosis of a long bleeding time with a normal platelet count is either von Willebrand's disease or a qualitative platelet defect, as shown in Table 6.[35] The possibility of von Willebrand's disease is further evaluated by testing for factor VIII antigen, factor VIII activity, ristocetin cofactor activity, and multimer analysis. If von Willebrand's disease has been ruled out, then the cause is a qualitative platelet defect. Most of the acquired qualitative platelet defects will be suggested by the history, review of the patient's medications, or by abnormalities of the CBC and peripheral smear.[36] Qualitative platelet defects are particularly common in the myelodysplastic syndromes and in renal failure. Those that occur in patients with myeloma and Waldenström's macroglobulinemia tend to be associated with elevated paraprotein levels and may respond to plasmapheresis. Patients with idiopathic thrombocytopenic purpura tend not to bleed even with platelet counts in the range of 10,000 to 20,000 per μl. Therefore, when a patient with idiopathic thrombocytopenic purpura appears to be having excessive bleeding for the number of platelets, the antiplatelet antibody may be interfering with platelet function in addition to causing accelerated platelet clearance.[37] These patients may respond to steroid therapy.

Platelet aggregation studies can separate the congenital platelet disorders. Patients with Bernard-Soulier disease have a deficiency of glycoprotein Ib and therefore have abnormal ristocetin-induced platelet aggregation but normal aggregation with adenosine diphosphate, collagen, epinephrine, thrombin, and arachidonic acid. Patients with Glanzmann's thrombasthenia, on the other hand, have deficient glycoproteins IIb and IIIa but normal Ib and therefore have normal ristocetin-induced aggregation but deficient aggregation with all the other agents. Both of these disorders can be further confirmed by specific assays for the membrane glycoproteins. There remains a large number of patients with unspecified qualitative platelet defects that are probably congenital. Many of these patients will only manifest abnormal bleeding following the ingestion of aspirin or a nonsteroidal anti-inflammatory drug. With the exception of uremia, myeloma, and antiplatelet antibody, the treatment of abnormal life-threatening bleeding for any other qualitative platelet defects is the transfusion of platelets. For less than life-threatening situations, administering desmopressin acetate may be useful.[38]

In evaluating a bleeding patient, the thrombin time, prothrombin time, PTT, platelet count, bleeding time, and peripheral smear findings will allow virtually all of the causes of abnormal bleeding to be diagnosed. There are, however, three categories of abnormal bleeding that would be missed by this panel of screening tests (Table 7).

TABLE 6.—*Differential Diagnosis of Long Bleeding Time With Normal Platelet Count, Thrombin Time, Prothrombin Time, and Partial Thromboplastin Time*

- Von Willebrand's disease—check factor VIII antigen, factor VIII activity, ristocetin cofactor activity, multimer analysis
- Qualitative platelet defect
  - Congenital
    - Bernard-Soulier disease
    - Glanzmann's thrombasthenia
    - Gray platelet syndrome
    - Unspecified
  - Acquired
    - Drug—aspirin, NSAIDs, alcohol
    - Uremia
    - Myeloproliferative syndrome
    - Myelodysplasia
    - Myeloma or Waldenström's macroglobulinemia
    - Antiplatelet antibody

NSAIDs=nonsteroidal anti-inflammatory drugs

Urea Clot Solubility

Conditions that allow fibrin polymer to be formed in a sufficient amount to stop the automated fibrometer but which do not allow covalent cross-linking of the polymer to form a definitive fibrin meshwork may cause abnormal bleeding. Factor XIII deficiency is a congenital disorder that classically causes umbilical bleeding in early life. In addition, patients with bleeding from the umbilicus commonly have platelet-type bleeding—superficial bruising, subcutaneous hematomas, bleeding from the mouth, nose, and gums—except that the bleeding tends to occur some hours after the trauma, more like a factor deficiency. Two other usual features of factor XIII deficiency are a significant incidence of intracranial bleeding, often with minimal or no trauma, and recurrent spontaneous abortion. There have been cases of abnormal fibrinogens that can form polymer but cannot be cross-linked, perhaps because of a loss of binding sites. Cases of acquired inhibitors of fibrin polymer cross-linking have also been described. Such inhibitors developed in four patients with clinical bleeding while they were on isoniazid therapy.[18] Factor XIII deficiency and disorders of fibrin cross-linking are screened for by a urea clot solubility test. Inadequate cross-linking results in early clot dissolution in 5 mol per liter urea. Because only 2% factor XIII activity is needed for adequate cross-linking and because factor XIII

TABLE 7.—*Causes of Abnormal Bleeding Not Detected by Thrombin Time, Prothrombin Time, Partial Thromboplastin Time, Platelet Count, or Bleeding Time*

- Poor fibrin polymer cross-linking
  - Factor XIII deficiency
  - Inhibitor of factor XIII
  - Abnormal fibrinogen
- Abnormal or excessive fibrinolysis
  - α_2-Antiplasmin deficiency
  - Increased tissue plasminogen activator (TPA)
  - TPA inhibitor deficiency
  - Urokinase
  - Primary fibrinolysis
- Vascular purpuras
  - Scurvy
  - Amyloid
  - Senile purpura
  - Vasculitis
  - Schönlein-Henoch purpura
  - Congenital connective tissue disorders—Marfan's syndrome, Ehlers-Danlos syndrome
  - Cryoglobulins
  - Autoerythrocyte purpura
  - Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia)

has a half-life of 10 to 14 days, recent whole blood or plasma replacement may cause a falsely normal result.

Euglobulin Clot Lysis Time

The second broad category of causes of abnormal bleeding not detected by routine screening tests is abnormal fibrinolysis (Table 7).[39] The normal scheme for fibrinolysis is shown in Figure 1. The cases of patients with congenital deficiency of α_2-antiplasmin and excesses of tissue plasminogen activator (TPA) have been reported. Patients with cirrhosis appear to have both decreased hepatic production of α_2-antiplasmin and decreased clearance of TPA.[40] With fibrinolytic therapy (streptokinase, urokinase, or TPA) when plasmin generation exceeds α_2-antiplasmin capacity, fibrinogenolysis as well as fibrinolysis occurs. It now appears that almost all cases of "primary fibrinolysis" are due to DIC.

Abnormalities of excessive fibrinolysis may be screened for with either a whole blood clot lysis time or the more rapid euglobulin clot lysis test. The normal value for euglobulin clot lysis is 1½ to 6 hours, and values shorter than this suggest excessive fibrinolysis (a low fibrinogen level will give a false-positive reading due to poor clot formation). This can then be further evaluated with specific α_2-antiplasmin and TPA levels. With the fibrin plate assay, plasma is added to plasminogen-containing and plasminogen-free fibrin-coated plates. Circulating plasmin will lyse both plates. Circulating tissue plasminogen activator will lyse only the plasminogen-containing plate.

Vascular Purpuras

The third category of disorders of apparent abnormal bleeding not detected by screening studies is the vascular purpuras (Table 7).[41] In these disorders, the coagulation factors and platelets are thought to function normally, but the defect lies in abnormal vascular fragility.

The Rumpel-Leede capillary fragility test is done by inflating a blood pressure cuff on the upper arm to 80 mm of mercury for five minutes. Cutaneous ecchymoses appearing below the cuff suggest abnormal vascular fragility. In most cases of vascular purpura, the bleeding time is normal.[42] Further evaluation may require a workup for vasculitis—erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, complements, immune complexes, cryoglobulins—and skin biopsy. A final group of rare bleeding disorders includes autoerythrocyte sensitization and factitial bleeding.[43]

Conclusion

The systematic approach to a patient with unexplained bleeding begins with the history and physical examination. Particular attention is given to elements of the personal or family history that would suggest a congenital bleeding disorder. In addition, it should be determined whether there is a coagulation factor or a platelet-type bleeding disorder and whether the bleeding is localized or generalized. Although it is useful to didactically describe a step-by-step approach to the laboratory evaluation of bleeding, frequently the workup must be telescoped because of the urgency for therapy, and some of the tests that need to be done should be carried out simultaneously. In virtually all cases, the evaluation begins with a thrombin time, prothrombin time, partial thromboplastin time, platelet count, and bleeding time (Table 8). There is a limited differential diagnosis for a long thrombin time, and clinicians must be particularly alert for DIC. An isolated prolongation of the prothrombin time or one that is prolonged out of proportion to the PTT with a normal thrombin time should always raise the possibility of vitamin K deficiency. If the thrombin time and prothrombin time are normal and the partial thromboplastin time is prolonged, a mixing study is then carried out. The results of this should lead to a limited differential diagnosis of either factor deficiency or inhibitor. If the thrombin time, prothrombin time, and PTT are normal, the platelet count is then evaluated. Thrombocytopenia is further evaluated by examining the CBC, a peripheral smear with special attention to microangiopathy, the medication list, and a bone marrow specimen. If the platelet count is normal and the bleeding time is prolonged with normal thrombin, prothrombin, and partial

TABLE 8.—*Overall Scheme for Laboratory Evaluation of a Bleeding Patient*

- History, physical examination, medication inquiry
- Basic screening studies
  - Thrombin time
  - Prothrombin time
  - Partial thromboplastin time (PTT)
  - Complete blood count, platelet count
  - Peripheral smear
  - Bleeding time
- Increased thrombin time
  - Rule out heparin contamination
    - Repeat venipuncture
    - Check patient's drug ingestion
    - Use in vitro protamine, reptilase time, toluidine blue, Heparsorb
  - Rule out disseminated intravascular coagulation (DIC)—check fibrinogen, fibrin degradation products, or D-dimer
    - Protamine paracoagulation
    - Platelet count, smear for microangiopathy
  - If low fibrinogen but not DIC, check immunologic fibrinogen; if > 2 × functional fibrinogen, dysfibrinogenemia is present
  - Mixing study on thrombin time
    - Serum protein electrophoresis for paraprotein
    - Antibody to thrombin
    - Heparinoid inhibitor
- Normal thrombin time, increased prothrombin time
  - Give vitamin K
  - Check liver function
  - Consider surreptitious use of sodium warfarin
  - Plasma washout
  - Factor VII deficiency
  - Deficiency or inhibitor of factor II, factor V, or factor X
  - Aspirin overdose
  - γ-Carboxylation enzyme deficiency
- Normal thrombin time and prothrombin time, prolonged PTT
  - See Table 3
- Normal thrombin time, prothrombin time, PTT, decreased platelet count
  - Check smear; if microangiopathic, see Table 4
  - Check hemoglobin, leukocyte count; if both decreased, do bone marrow study
  - Check drugs (see Table 5)
- Normal thrombin time, prothrombin time, PTT, platelets, increased bleeding time
  - See Table 6
- Urea clot solubility
- Euglobulin clot lysis time
- Vascular fragility
- Consider autoerythrocyte sensitization or factitious bleeding

thromboplastin times, the differential diagnosis is either von Willebrand's disease or a qualitative platelet defect. The above studies will characterize the abnormal bleeding in more than 95% of patients. The remainder have either poor fibrin polymer cross-linking, abnormal or excessive fibrinolysis, or increased vascular fragility. With the use of these screening tests and follow-up studies, virtually all causes of abnormal bleeding can be characterized, both common and uncommon, and specific therapy determined.

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Medical Progress

Modern Vestibular Function Testing

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Current tests of vestibular function concentrate on the horizontal semicircular canal-ocular reflex because it is the easiest reflex to stimulate (calorically and rotationally) and record (using electro-oculography). Tests of the other vestibulo-ocular reflexes (vertical semicircular canal and otolith) and of the vestibulospinal reflexes have yet to be shown useful in the clinical setting. Digital video recording of eye movements and vestibular-evoked responses are promising new technologies that may affect clinical testing in the near future.

(Baloh RW, Furman JMR: Modern vestibular function testing. West J Med 1989 Jan; 150:59-67)

As with other sensory systems, there are two general categories of tests of vestibular function: those relying on the subjective response of a patient and those relying on objective measurements of reflex activity. Unlike tests of the auditory and visual systems, however, quantifying the sensation of movement derived from excitation of the vestibular receptors has been a difficult task for clinicians.[1] It is often impossible for a patient to differentiate those sensations that are strictly vestibular from visual and proprioceptive sensations. Equally important, the subjective awareness of vestibular stimulation depends on a patient's general state of alertness and degree of cooperation. For these reasons, modern vestibular function testing has focused on objective measurements of vestibular reflex activity. The horizontal semicircular canal-ocular reflex has received the most attention to date because there are several relatively simple techniques for stimulating and recording it. In the future, the clinical assessment of vestibular function must include tests of the other suborgans of the vestibular apparatus, namely, the vertical semicircular canals and otolith organs.

Electronystagmography

Methods of Recording Eye Movements

Electro-oculography (EOG) is the simplest and most readily available method for recording eye movements.[2] With this technique, a voltage surrounding the orbit is measured whose magnitude is proportional to the amplitude of the eye movement. When used for evaluating vestibular function, the technique has been termed electronystagmography (ENG), and often the terms EOG and ENG are used interchangeably.[3-5] With EOG the velocity, frequency, and amplitude of spontaneous or induced nystagmus and the changes in these measurements brought about by a loss of fixation—either with the eyes closed or with the eyes open in darkness—can be quantified. Also, visually guided eye movements (saccadic and pursuit) can be quantitatively assessed.

The principle of electro-oculography is shown in Figure 1.[6] The pigmented layer of the retina maintains a negative potential with regard to the surrounding tissue by means of active ion transport. The potential difference between the cornea and the retina, known as the corneoretinal potential, acts as an electric dipole oriented in the direction of the long axis of the eye. In relation to a remote electrode, an electrode placed in the vicinity of the eye becomes more positive when the eye rotates towards it and less positive when it rotates in the opposite direction. With EOG, the measured voltage is proportional to the sine of the angle of motion.

The advantages of EOG are that it is relatively inexpensive, easily administered, noninvasive, does not interfere with vision, and does not require head restraint. It is reasonably accurate, even for the large horizontal eye movements that are encountered during routine vestibular and ocular motor testing. The disadvantages of EOG include the inability to accurately measure vertical eye movements, interference of eye-blink artifacts,[7] poor signal to noise ratio, susceptibility to changes in skin resistance caused by perspiration, and a dependence on lighting conditions in the test room.[8,9]

Table 1 compares the characteristics of EOG with those of three other eye movement recording techniques that are currently used, primarily in research.[10-14] These other techniques are more sensitive than EOG but at present are not practical for routine ENG testing. The direct video recording of eye movements is the newest and most promising of these techniques. A video camera is used that interfaces with a digital computer. At regular intervals images are stored by the computer for subsequent data analysis.[13] Specialized algorithms for digital signal processing are then used to determine horizontal and vertical eye positions. With the rapid advances occurring in this area, it is reasonable to expect that the sensitivity will improve and the costs will decrease in the near future.

Electronystagmography can be used to evaluate many types of eye movement disorders by adapting the testing procedure for specific abnormalities. It is useful, however, to have a standard test battery that screens all important areas. A typical test battery includes tests for pathologic nystagmus, vestibulo-ocular reflex function (usually the bithermal caloric test), and visual ocular control (saccades and smooth pursuit).

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ABBREVIATIONS USED IN TEXT

ENG = electronystagmography
EOG = electro-oculography
VOR = vestibulo-ocular reflex
VOR-Fix = VOR with fixation-suppression
VVOR = visual vestibulo-ocular reflex

Recording for Pathologic Nystagmus

Pathologic nystagmus may be spontaneous (present in the primary position with the patient seated), positional (induced by a change in head position), or gaze-evoked (induced by a change in eye position).[6]

Spontaneous nystagmus of peripheral vestibular origin is strongly suppressed with fixation and usually is not evident on routine examination unless a patient is seen within a week of the acute incident (Table 2). By contrast, peripheral vestibular nystagmus can be recorded with patients' eyes closed or with their eyes open in darkness and for as long as five to ten years after an acute peripheral vestibular lesion. About 10% to 20% of normal subjects will have a low-velocity spontaneous nystagmus with eyes closed or with eyes open in darkness—less than 3 degrees per second.[5,15] As a general rule, spontaneous nystagmus present with fixation—that is, seen on routine examination—that persists for more than a week is a central sign. Congenital spontaneous nystagmus is usually easily differentiated from acquired central vestibular nystagmus because the former has a high frequency and variable waveform and has been present since infancy.

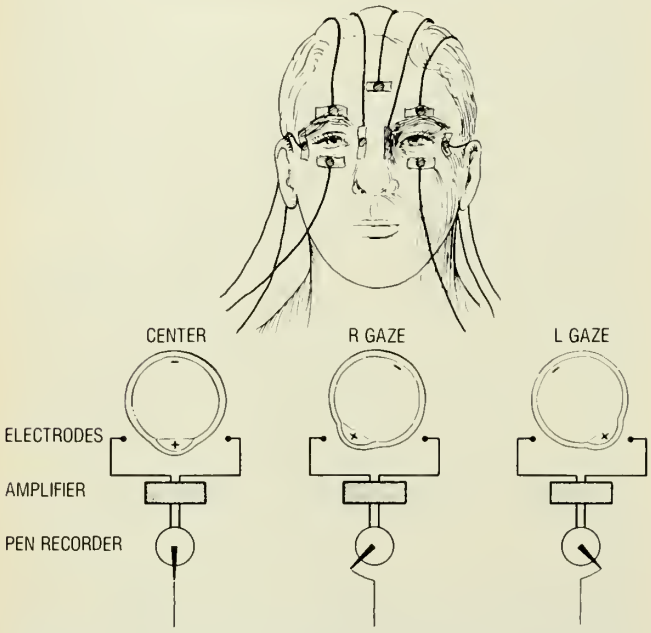

Figure 1.—The technique of electro-oculography is shown (from Baloh[6]).

Positional nystagmus can be static or paroxysmal (Table 3). Static positional nystagmus is induced by slowly placing the patient in the supine, right lateral, and left lateral positions. This type of positional nystagmus persists as long as the position is held. Paroxysmal positional nystagmus, on the other hand, is induced by a rapid change from the erect sitting to the supine head-hanging left, center, or right positions. It is initially high in frequency but rapidly dissipates within 30 seconds to 1 minute.

The most common variety of paroxysmal positional nystagmus—so-called benign positional nystagmus—usually has a 3- to 10-second latency before it begins and rarely lasts longer than 15 seconds. The nystagmus has linear and torsional components with the fast component directed upward—that is, towards the forehead.[16] A key feature is that patients experience severe vertigo with initial positioning but with repeated positioning, vertigo and nystagmus rapidly disappear. By contrast, paroxysmal positional nystagmus of central origin typically does not decrease in amplitude or duration with repeated positioning, does not have a clear latency, and usually lasts longer than 30 seconds.[17] The direction is unpredictable and may be different in different positions. It is often truly vertical with the fast component directed downward—that is, towards the cheeks.

Static positional nystagmus is a common finding both in normal subjects and patients when eye movements are recorded with their eyes open in darkness or with their eyes closed. As in the case of spontaneous nystagmus, however, the average slow-phase velocity of static positional nys-

TABLE 1.—*Important Features of Different Eye Movement Recording Techniques*

	Eye Movement Recording Techniques			
Feature	*Electro-oculography*	*Infrared Reflection*	*Scleral Search Coil*	*Video**
Recording device	Paste-on electrodes	Photovoltaic diodes on glasses	Coil inside contact lens	Video camera
Principle	Corneoretinal potential	Differential reflection of iris and sclera	Electric current induced in coil	Digital processing of video image
Range of horizontal eye movement, degree	±40	±10-15	Unlimited	Unlimited
Range of vertical eye movement, degree	±30	±5-10	Unlimited	Unlimited
Range of torsional eye movement	...	...	Unlimited	Unlimited
Approximate accuracy, degree	1-2	0.5	0.01	1
Approximate cost, $†	2,000	8,000	20,000	100,000
Will record when patient's eyes closed	Yes	No	Yes	No
Able to record normal vision	Yes	Yes	Yes	Yes
Able to record during head movement	Yes	No	Yes	Yes
Susceptible to eye-blink artifacts	Yes	Yes	Yes	Yes
Sensitive to changes in room lighting	Yes	No	No	No
Sensitive to electrical interference	Yes	Yes	Yes	No
Sensitive to electromyographic interference	Yes	No	No	No

*Computer analyzed video recordings.
†Including electronic amplifiers, if needed.

tagmus in normal subjects does not exceed 3 degrees per second.[15,18,19] The nystagmus may be unidirectional in all positions or direction-changing in different positions. Both direction-changing and direction-fixed types of static positional nystagmus occur most commonly with peripheral vestibular disorders, but both also occur with central lesions.[19] Their presence only indicates a dysfunction in the vestibular system without a localizing value. As with spontaneous nystagmus, however, a lack of suppression with fixation and signs of associated brain-stem dysfunction suggest a central lesion.

Gaze-evoked nystagmus is induced by having a patient fixate on a target 30 degrees to the right, left, above, and below the center position. Eye position should be held for at least 30 seconds. A gaze deviation beyond 40 degrees should be avoided because it may result in nystagmus even in normal subjects ("end-point nystagmus"). Normal subjects can have gaze-evoked nystagmus in the dark or with eyes closed, but gaze-evoked nystagmus recorded with fixation is always an abnormal sign.

Symmetric gaze-evoked nystagmus is most commonly produced by the ingestion of drugs such as phenobarbital, phenytoin, alcohol, and diazepam. It can also occur in patients with such varied conditions as myasthenia gravis, multiple sclerosis, and cerebellar atrophy.[1] Asymmetric horizontal gaze-evoked nystagmus always indicates a structural brain-stem or cerebellar lesion, with the lesion usually on the side of the larger amplitude nystagmus ("Bruns's nystagmus").[20] Rebound nystagmus is a type of gaze-evoked nystagmus that either disappears or reverses direction as an eccentric gaze position is held. When the eyes are returned to the primary position, nystagmus occurs in the direction of the return saccade. Rebound nystagmus is the only variety of nystagmus thought to be specific for cerebellar involvement.[21,22]

Bithermal Caloric Testing

The caloric test uses a nonphysiologic stimulus to induce endolymphatic flow in the horizontal semicircular canal and thus horizontal nystagmus by creating a temperature gradient from one side of the canal to the other. Unfortunately, because of their position in the temporal bone, the vertical semicircular canals cannot be reliably activated by a caloric stimulus.

With bithermal caloric testing each ear is irrigated with a constant flow rate of water that is 7°C below body temperature (30°C [86°F]) and 7°C above body temperature (44°C [111°F]). The patient lies in the supine position with the head tilted 30 degrees forward so that the horizontal semicircular canals are in the vertical plane. Recordings are made with the patient's eyes open behind Frenzel glasses or in total darkness. Recording with patients' eyes closed is not recommended since eye closure can suppress vestibular nystagmus in some subjects; in others, lid artifacts are prominent.[23] From the ENG recordings, the maximum slow-phase velocity is calculated for a five- to ten-second interval at the peak of response. Slow-phase velocity is a much more sensitive indicator of vestibular function than either the duration or frequency of the caloric response.[24]

The four responses of a bithermal caloric test are routinely compared with two standard formulas. The vestibular paresis formula,

$$\frac{(L\,30°C + L\,44°C) - (R\,30°C + R\,44°C)}{L\,30°C + L\,44°C + R\,30°C + R\,44°C} \times 100,$$

compares the right-sided responses with the left-sided responses, and the directional preponderance formula,

$$\frac{(L\,30°C + R\,44°C) - (L\,44°C + R\,30°C)}{L\,30°C + R\,44°C + L\,44°C + R\,30°C} \times 100,$$

compares nystagmus to the right with nystagmus to the left in the same person. In both of these formulas, the difference in response is reported as a percentage of the total response. This is important because the absolute magnitude of caloric response is dependent on several factors, including age. Dividing by the total response normalizes the measurements to remove the large variability in absolute magnitude of normal caloric responses. In our laboratories, the upper normal value for vestibular paresis is 22%, while that for directional preponderance is 28% (using the maximum slow-phase velocity in the above equations).[15]

A caloric fixation-suppression index can be obtained by having a patient fixate on a target during the middle of the response. Because the slow-phase velocity of caloric-induced nystagmus is constantly changing, it is important that the fixation period occur near the time of maximum

TABLE 2.—*Types of Spontaneous Nystagmus*

Nystagmus Type	*Description*	*Location of Lesion*
Peripheral vestibular	Combined horizontal-torsional, inhibited with fixation except in acute stage (<1 week)	Labyrinth or vestibular nerve
Central vestibular	Pure horizontal, vertical, or torsional not well inhibited with fixation	Central vestibular pathways—brain stem and cerebellum
Congenital	High-frequency variable waveform present since infancy	Unknown, no structural correlate

TABLE 3.—*Types of Positional Nystagmus*

Nystagmus Type	*Description*	*Locating Lesion*
Paroxysmal Positional		
Peripheral	Torsional up-beat, brief (<30 sec), fatigability, usually prominent in only one position	Labyrinth, probably posterior semicircular canal
Central	Pure horizontal or vertical, persists (>30 sec), no fatigue, prominent in multiple positions	Fourth ventricular region
Static Positional		
Peripheral	Combined horizontal-torsional, inhibited with fixation except in acute stage	Labyrinth or vestibular nerve
Central	Pure horizontal, vertical, or torsional, not inhibited with fixation	Central vestibular pathways—brain stem and cerebellum

response to obtain the best estimate of fixation-suppression. The fixation-suppression index is defined as the average slow-phase velocity with fixation divided by the average slow-phase velocity without fixation × 100. In normal subjects, the average visual-suppression index is 48% ± 10%.[25]

Abnormal findings on the bithermal caloric test are summarized in Table 4. As a general rule, a substantial vestibular paresis indicates a peripheral vestibular lesion (including the nerve root entry zone), while a substantial directional preponderance is nonlocalizing—that is, it can occur with peripheral and central lesions. The caloric test is relatively insensitive for identifying bilateral vestibular lesions, such as those caused by ototoxic drugs. Because of the wide range of normal values for a maximal slow-phase velocity—5 to 100 degrees per second in our laboratory—a patient's value may decrease severalfold before falling below the normal range.[24] Lesions of the cerebellum occasionally can lead to bilateral increased caloric responses, but again because of the wide range of normal values, it is rare to find caloric responses that exceed the upper normal range. Impaired fixation-suppression of caloric-induced nystagmus indicates a central nervous system lesion, most commonly a lesion involving the midline cerebellum.

Saccades and Smooth Pursuit

Along with the vestibulo-ocular reflexes, two visually controlled ocular stabilizing systems produce conjugate eye movements—the saccadic and smooth pursuit.[26] The saccadic system responds to a retinal position error to bring a peripheral target to the fovea in the shortest possible time. The smooth pursuit system maintains gaze on a moving target by generating a continuous match of eye and target velocity. Optokinetic nystagmus is a form of smooth pursuit in which eye tracking motion in one direction is periodically interrupted by corrective saccades in the opposite direction to relocate the gaze onto new targets coming into the visual field. Saccadic and pursuit eye movements are typically induced by having a patient follow a target moving in a stepwise and a sinusoidal pattern, respectively. For optokinetic testing, a striped pattern is moved across the patient's visual field in a clockwise and counterclockwise direction. With ENG, features of these visually controlled eye movements can be accurately measured and the results compared with normative data. Typically measured are the peak velocity, accuracy, and reaction time of saccadic eye movements.[27] For pursuit and optokinetic nystagmus, the tracking eye velocity is compared with the target or optokinetic drum velocity.[27]

Abnormalities of visual ocular control are helpful for localizing lesions of the central nervous system (Table 5).[28] With one exception, peripheral vestibular lesions do not impair visual ocular control. After an acute unilateral labyrinthine or vestibular nerve lesion, smooth pursuit and optokinetic nystagmus slow-phase velocity will be transiently decreased to the contralateral side—that is, in the direction of the spontaneous nystagmus. The asymmetry of smooth pursuit and optokinetic nystagmus disappears in a few weeks despite the persistence of the vestibular nystagmus in the dark.

Rotational Testing of the Horizontal Semicircular Canals

Rotational testing of the horizontal vestibulo-ocular reflex is becoming more widely used because modern motor-driven platforms can be precisely controlled and multiple graded stimuli can be delivered in a relatively short time. In addition, rotatory testing is often less bothersome to patients than caloric testing. Unlike caloric testing, rotatory testing depends only on the inner ear and is unrelated to the physical features of the external ear or temporal bone. Thus, rotational testing is a more reliable vestibular stimulus. A major disadvantage of rotational testing is that both ears are stimulated simultaneously so that it is less useful than caloric testing for identifying unilateral peripheral vestibular lesions.

TABLE 4.—*Interpreting the Results of a Bithermal Caloric Test*

Result	*Description*	*Location of Lesion*
Vestibular paresis	>22%* asymmetry between right- and left-sided responses	Unilateral labyrinth, vestibular nerve, including root entry zone
Directional preponderance	>28%* asymmetry between left-beating and right-beating nystagmus	Nonlocalizing (anywhere in peripheral and central vestibular pathways)
Bilateral hypoactive	Slow-component velocity <5 degrees/sec bilaterally	Bilateral labyrinth, vestibular nerves, including root entry zones
Impaired fixation-suppression	Fixation does not produce at least 50% decrease in maximum slow-component velocity	Central—brain stem and midline cerebellar

*Normal values for UCLA, each laboratory should establish normative data.

TABLE 5.—*Summary of Visual Ocular Control Abnormalities Produced by Focal Neurologic Lesions*

Location of Lesion	*Saccades*	*Smooth Pursuit and Optokinetic Nystagmus Slow Phase*
Cerebellopontine angle	Ipsilateral dysmetria*	Progressive ipsilateral impairment
Diffuse cerebellar	Bilateral dysmetria	Bilateral impairment
Intrinsic brain stem	Decreased maximum velocity, increased delay time	Ipsilateral or contralateral impairment
Basal ganglia	Hypometria,† increased delay time (bilateral)	Bilateral impairment
Frontoparietal cortex	Contralateral hypometria	Normal
Parieto-occipital cortex	Normal	Ipsilateral impairment

*Undershoots and overshoots.
†Undershoots only.

For rotational testing in our laboratories, a patient is seated in a chair mounted on a motorized rotating table placed inside a light-tight electrically shielded room.[29] For EOG calibration, an array of three light-emitting diodes spaced at the center and 15 degrees to the right and left is attached to a chair directly in front of the patient. Frequent calibrations are interspersed throughout the testing procedure to correct for any fluctuations in the corneoretinal potential. The rotatory chair, a surrounding optokinetic drum, and calibration lights are all controlled by the same microprocessor that analyzes the nystagmus response.

The vestibular system is tested by rotating the chair sinusoidally—in the dark (vestibulo-ocular reflex, or VOR), in the light with the optokinetic drum stationary (visual vestibulo-ocular reflex, or VVOR), and in the dark with the center light-emitting diode lit (VOR with fixation-suppression, or VOR-Fix). In the first instance, the vestibular system is tested without visual influence, whereas in the second, the vestibular and optokinetic systems are stimulated in a synergistic fashion; in the third, the pursuit system is used to suppress vestibular-induced nystagmus. The computer generates stimulus signals at frequencies ranging from 0.0125 to 1.6 Hz and peak velocities of 15 to 100 degrees per second. For screening purposes, we routinely use 0.05 Hz and a peak velocity of 60 degrees per second.

Typical responses of a normal subject to optokinetic and the three standard rotational tests are shown in Figure 2, left panel. In each case, the peak stimulus velocity is 60 degrees per second. All responses are symmetric. The mean gain (defined as peak slow-phase velocity divided by peak stimulus velocity) $\pm$ 1 standard deviation for similar testing in 20 normal subjects is as follows: optokinetic nystagmus, 0.83 $\pm$ 0.13; VOR, 0.50 $\pm$ 0.15; VVOR, 0.99 $\pm$ 0.05; VOR-Fix, 0.03 $\pm$ 0.02.

Patients with unilateral lesions of the labyrinth or eighth nerve have two characteristic abnormalities on VOR testing; they show an asymmetric gain—that is, a decreased slow-phase velocity with rotation towards the side of the lesion—and an increased phase lead (abnormal timing) of eye velocity relative to stimulus velocity at low frequencies of rotation, 0.05 Hz and lower (Figure 2, center panel).[30] The asymmetry of response is most pronounced with acute lesions and often disappears as recovery occurs, whereas the abnormal timing at low frequencies remains indefinitely.[31] With bilateral peripheral vestibular lesions, the VOR responses are symmetrically decreased or absent at low frequencies (Figure 2, right panel), although VOR responses may be preserved at higher frequencies. As a general rule, optokinetic nystagmus and visual-vestibular interaction tests are normal in patients with peripheral vestibular lesions although a transient asymmetry can occur if there is a strong spontaneous nystagmus.

As opposed to patients with peripheral vestibular lesions, patients with central nervous system lesions usually have abnormalities of visual vestibular interaction. Three characteristic abnormal patterns on the standard rotational test battery are shown in Figure 3. Lesions of the lateral medulla involving the vestibular nuclei characteristically affect both visual and vestibulo-ocular responses.[32] Often the optokinetic nystagmus gain is greater towards the side of the lesion, whereas the VOR gain is greater away from the side of the lesion. Fixation-suppression of the VOR is uniformly impaired, particularly slow phases towards the side of the lesion. Patients with lesions involving the vestibulocerebellum have severely impaired optokinetic responses.[33] The gains of their VOR, VVOR, and VOR-Fix responses are approximately the same—that is, these patients are unable to modulate their vestibulo-ocular reflex with vision. Finally, lesions of the visual motor pathways from the parietal-occipital cortex to the horizontal gaze center in the pons impair ipsilateral visual following responses—smooth pursuit and optokinetic nystagmus slow phases—without affecting VOR responses.[34] Fixation-suppression of contralateral VOR slow phases is impaired because pursuit in one direction is used to inhibit VOR slow phases in the opposite direction.

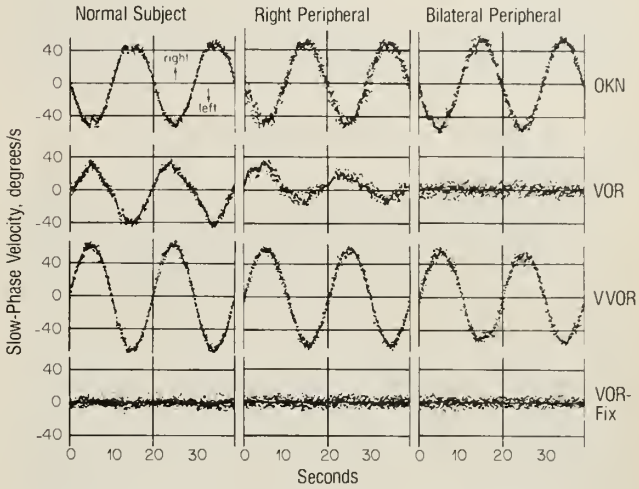

Figure 2.—The plots show slow-phase velocity versus time for optokinetic nystagmus (OKN) and sinusoidal rotational tests (0.05 Hz, peak velocity 60 degrees per second) in a normal subject **(left)**, a patient who underwent right labyrinthectomy **(center)**, and a patient with bilateral vestibulopathy due to using ototoxic drugs **(right)** (from Baloh et al[29]). VOR = vestibulo-ocular reflex, VVOR = visual VOR, VOR-Fix = VOR with fixation-suppression

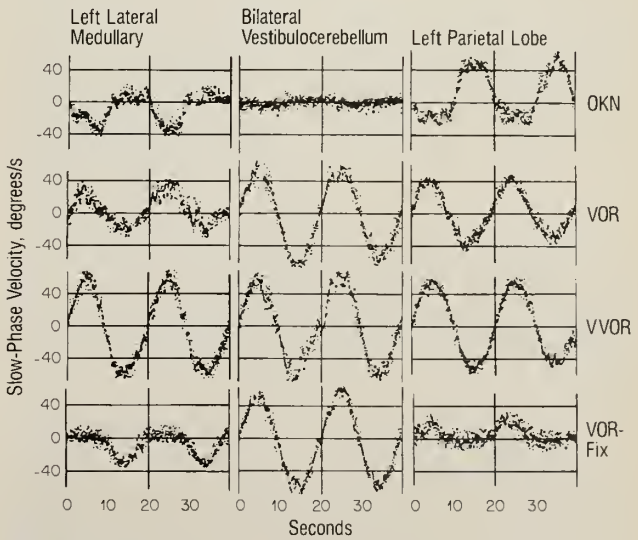

Figure 3.—The plots show slow-phase velocity versus time for optokinetic nystagmus (OKN) and the four standard sinusoidal rotational tests (0.05 Hz, peak velocity 60 degrees per second) in a patient with infarction of the left lateral medullary region **(left)**, a patient with caudal midline cerebellar atrophy **(center)**, and a patient with glioma in the deep parietal lobe on the left side **(right)**. VOR = vestibulo-ocular reflex, VVOR = visual VOR, VOR-Fix = VOR with fixation-suppression

TABLE 6.—*Vestibular Tests and the Suborgans They Stimulate**

Test	Semicircular Canals: Horizontal	Semicircular Canals: Vertical	Otoliths
Conventional rotatory chair	×	...	...
Pitch rotation			
Upright	...	×	×
On-side	...	×	...
Ocular counterrolling			
Static	...	...	×
Dynamic	...	×	×
Eccentric rotation	×	...	×
Off-vertical rotation	×	...	×
Linear track	...	...	×
Parallel swing	...	...	×

*× denotes stimulation.

Tests of the Vertical Semicircular Canals and Otoliths

As noted, vestibular tests that are in current use evaluate only the horizontal semicircular canals. Future tests, designed to evaluate other vestibular suborgans—the vertical semicircular canals and otolith organs—will require movements that stimulate these receptors singly or in combination.[35] The determination of which vestibular suborgans are stimulated by a particular movement is often complex and requires a knowledge of three factors: whether the stimulus is an angular or a linear acceleration, the orientation of the skull (and thus the labyrinth) with respect to the movement, and the orientation of the movement with respect to gravity. Table 6 lists the tests we will describe and indicates which suborgans the various tests are designed to evaluate.

Pitch Rotation

Rotating the head in the sagittal plane—like nodding the head "yes"—stimulates all four vertical semicircular canals. If the pitch stimulus is delivered with the subject seated in the upright position (upright pitch), the head changes its orientation with respect to gravity as it tips forward and backward. This change in orientation with respect to gravity stimulates the otolith organs in addition to the vertical semicircular canals. If, however, a subject is seated in a conventional rotatory chair with the head tilted towards the shoulder so that one ear is down, the orientation of the subject with respect to gravity will not change during rotation and the otoliths will not be stimulated. This stimulus, called "on-side" pitch, is thus comparable to conventional rotation described above, except that for on-side pitch rotation, the vertical rather than the horizontal semicircular canals are stimulated.

There are major limitations to the use of pitch rotation clinically because of problems with delivering the stimulus and measuring the response. Although on-side pitch can be delivered with only minor modifications of a conventional rotatory chair, upright pitch requires cumbersome and costly equipment. Moreover, the vertical eye movements that are induced by pitch rotation cannot be measured accurately with EOG; rather, either the magnetic scleral search coil or a video recording system is used. Preliminary studies in normal animals and humans indicate that there is a difference in the vestibulo-ocular responses to pitch between the upright and the on-side positions.[36–38] The gain was decreased and asymmetries were present in the latter compared with the former.

Ocular Counterrolling

The otolith-ocular reflex produces torsional eye movements during static head tilts. Rotating the head towards the right shoulder causes the eyes to counterrotate to the left, and rotating the head towards the left shoulder causes the eyes to counterrotate to the right. Such rotation of the head in the coronal plane is called roll and the counterrotation of the eyes is called ocular counterrolling.[39–41] To complicate matters, dynamic roll movements also stimulate the vertical semicircular canals because of the angular acceleration of the movement. Thus, when using roll stimulation, a distinction should be made between static and dynamic ocular counterrolling.

As with pitch rotation, the use of ocular counterrolling clinically is hampered by difficulties both in delivering the stimulus and in measuring the response. For patients to be rotated in their coronal plane, they must be securely fastened to a cumbersome and costly device. In addition, the amount of torsional eye movement produced by a static tilt in the coronal plane is relatively small. For example, if the head is tilted 45 degrees, the eyes counterroll only about 7 degrees. Electro-oculography and infrared reflection techniques are insensitive to this type of movement so that photographic or video recording or the magnetic scleral search coil must be used.

To date, several studies have indicated that unilateral peripheral vestibular lesions produce asymmetries in static ocular counterrolling.[42–44] Further research is needed, however, to determine the reliability of this technique in clinical vestibular laboratories.

Eccentric Rotation

Eccentric (off-center) rotation is delivered by seating a subject upright in a conventional rotatory chair so that the head is away from the axis of rotation, as if the head were placed at the end of the arm of a centrifuge. During angular acceleration with the head eccentric, the labyrinth is exposed to both a rotational and a linear acceleration and thus both the otolith organs and the horizontal semicircular canals are stimulated. Once a constant angular velocity is achieved, only the otoliths are stimulated. A complexity in fully describing this vestibular stimulus arises from the fact that the net linear acceleration delivered to a subject is the vector summation of the linear acceleration produced by the movement itself and the linear acceleration produced by gravity. The advantages of eccentric rotation are that conventional rotatory chairs (with minor modifications) and EOG methods can be used for this test.

With sinusoidal angular acceleration, the eye movements induced with the head at the center of rotation are compared with those induced during eccentric rotation, the difference being caused by the otolith organs.[45] Preliminary studies suggest that this might be a useful clinical test of the otolith-ocular reflex.[46] An even simpler test of otolith function is to have the patient estimate the subjective vertical—using a vertical light bar—during constant-velocity eccentric rotation.[47] Unlike other tests of subjective vestibular sensation, the sensation of tilt experienced during eccentric rotation appears to be highly reproducible. Patients with unilateral peripheral

vestibular lesions experience less of a sensation of tilt when the damaged ear is outermost.[47]

Linear Acceleration on Sleds

Another technique that has been used to study otolithic function in research laboratories is to deliver a pure linear acceleration on a linear track.[48,49] The device typically consists of a roller-coasterlike sled that runs along a track. As with eccentric rotation, the otolith organs sense the net linear acceleration—that is, the vector summation of the linear acceleration induced by the sled itself and that induced by gravity. For a relatively simple case in which the subject is placed on the sled facing the side as if looking out of the side window of an automobile moving forward, a consistent horizontal eye movement (including nystagmus) can be recorded with EOG. For other head orientations, vertical or torsional eye movements are induced, requiring other eye movement recording techniques such as the magnetic scleral search coil or a video system. The use of linear sleds clinically would be severely limited by the expense and size of the equipment.

Parallel Swing

The parallel swing is a simple technique for inducing linear acceleration that may be practical in a clinical laboratory.[50,51] It consists of a platform suspended from the ceiling by supporting cables at each of its four corners. For small-amplitude displacements, almost pure horizontal linear acceleration is experienced by a subject seated on the platform. As with a linear sled, the eye movement response on a parallel swing depends on the orientation of the subject's head relative to the linear acceleration of the swing and gravity. Thus, various combinations of horizontal, vertical, and torsional eye movements may be induced. Preliminary studies indicate that horizontal eye movements are reliably induced when normal human subjects are seated in the dark facing the side so that the linear acceleration occurs along the interaural axis.[50,51] Patients with bilateral peripheral vestibular lesions have diminished or absent responses.[51]

Off-Vertical Rotation

The off-vertical rotation test is done by seating the subject in a conventional rotatory chair and then tilting the entire apparatus, including the chair and subject.[52,53] In this way, as the subject rotates, the head is continually changing its orientation with respect to gravity. In the extreme case, in which the chair is tipped completely on its side (earth horizontal axis or "barbecue rotation"), the subject is rotated from supine to lateral to prone to lateral, and so on. Once a constant velocity is achieved, only the otolith organs are stimulated as the canals respond only to angular acceleration.

A major advantage of this type of otolith test is that a conventional rotatory chair can be used if the angle of the inclination is kept small. Subjects can be placed in or removed from the apparatus easily, and conventional EOG can record the eye movements because they are largely horizontal. A disadvantage is that the stimulus often produces nausea.

Off-vertical rotation testing using a constant velocity in normal subjects induces two horizontal eye movement components, a bias and a modulation component. In patients with unilateral peripheral vestibular lesions, the bias component is diminished when a patient rotates towards the involved ear, while the modulation component remains unchanged.[54,55]

Summary of Vertical Semicircular Canal and Otolith Tests

The tests of the vertical semicircular canal and otolith function briefly described are all based on the knowledge that the vertical semicircular canals sense angular acceleration in the coronal and sagittal planes and the otoliths sense linear acceleration in all directions. Each test induces a combination of horizontal, vertical, and torsional eye movements depending on the characteristics of the movement, the orientation of the subject with respect to the movement, and the orientation of the movement with respect to gravity. Further research is needed to determine the potential clinical usefulness of these investigational techniques.

Vestibulospinal Testing

The neural pathways that underlie the vestibular contribution to the control of head, body, and limb positions are collectively called the vestibulospinal system.[56] As noted, current vestibular laboratory tests concentrate on the vestibulo-ocular system; the vestibulospinal system has been relatively neglected. A major reason for this neglect is that it is difficult to accurately assess the role of the vestibulospinal system in isolation from other sensory systems, namely, vision and somatosensation.

Static Force Plates

The simplest method of recording human postural sway uses a so-called force plate. There are several devices of this type, each designed with the basic idea of recording the position of a subject's center of mass when upright. In fact, these devices measure the position of the center of force, which is a good estimate of the position of the center of mass if a body is moving slowly. The major limitation of such devices relates to the following: the nervous system uses a combination of sensory modalities during the maintenance of an upright stance, and static force plates do not yield controlled stimulus-response measures of vestibulospinal function and thus must rely on spontaneous movements of the body. This latter consideration is analogous to assessing the vestibulo-ocular system by simply monitoring eye position in the absence of vestibular stimulation. Measuring postural sway might be useful as a screening test for imbalance, but the information it provides is nonspecific and probably not helpful for identifying vestibular lesions.[57,58]

Moving Platform Posturography

Moving force platforms have been designed to overcome the limitations of static force platforms discussed above both by controlling the relative contributions of the visual, somatosensory, and vestibular inputs that are normally used to maintain an upright posture and by incorporating stimulus-response measures. With such a device, the platform on which a subject stands can be moved simultaneously with the visual surround. By coupling the platform to the sway of the subject, it is possible to maintain a constant angle between the foot and lower leg, thereby reducing a major source of somatosensory input to the postural control system.[59] If the subject closes his or her eyes or if the movement of the visual enclosure is coupled to body sway, the subject is also deprived of visual information about postural sway. In this way, the influence of the labyrinth on the upright posture through the vestibulospinal system can be studied in a more or less isolated manner.[60] A disadvantage of this technique is that during postural sway, many of the suborgans of the vestibular

labyrinth are stimulated simultaneously, including the vertical semicircular canals and the otolith organs. For this reason, moving platform studies are incapable of providing an assessment of the individual suborgans of the vestibular labyrinth. To date, moving force platform studies have indicated that a bilateral reduction in peripheral vestibular function results in abnormal postural sway when the device is operated to isolate the vestibulospinal system.[61] More research is required, however, to determine the usefulness of moving force platforms for routinely assessing the vestibulospinal system.

Vestibular Evoked Potentials

The ability to record a human vestibular evoked potential has obvious merits as it would provide an objective measure of peripheral vestibular function that would be independent of either the ocular motor or postural control systems. Despite the fact that sensory evoked potentials using auditory, visual, and somatosensory inputs have been developed and are in routine clinical use, short-latency vestibular evoked potentials have been recorded successfully only in small laboratory animals.[62,63] This lack of development is related to the difficulty in delivering a vestibular stimulus that is capable of triggering a coordinated volley of neural activity, a requirement for eliciting a measurable evoked potential. The vestibular equivalent of an auditory click, visual flash, or somatosensory prick is a brief, abrupt, high-intensity rotation equivalent to the rotation encountered during a blow to the face—an angular acceleration in the range of 7,000 degrees per second squared.

Prior research regarding human vestibular evoked potentials has focused on recording long-latency cortical potentials rather than brain-stem evoked potentials.[64-67] The results of these studies are conflicting; it is still unclear whether the recorded potentials are specific for the vestibular stimulus. Considering their possible clinical usefulness, research on vestibular evoked potentials will undoubtedly continue.

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Travelers' Diarrhea

If you take a group of travelers from the United States to Mexico, you can show that a prophylactic antibiotic such as trimethoprim-sulfamethoxazole will prevent gastroenteritis in the treated group versus the placebo group. I don't think there's any doubt about that. (Studies show that Pepto-Bismol does the same thing.) The problem with making the recommendation generically and having all travelers carrying around a 7-day, a 10-day, or 2-week supply of trimethoprim-sulfamethoxazole is that it will lead to resistance and lessen the use of a very valuable drug combination. Most gram-negative rods are sensitive to trimethoprim-sulfamethoxazole, including the *E coli* in your own GI tract, and you may run into a *Salmonella* or a *Shigella* which is resistant to the trimethoprim-sulfamethoxazole. So now you've ingested a salad that has a *Shigella sonnei* or a *Shigella dysenteriae,* worse yet. And you are taking an antibiotic that is wiping out your own normal flora, which does have some counterbalancing effect in your fight against invading pathogens. And not only that, the antibiotic that you're taking is not effective against the organism that you've run into because it is resistant to the trimethoprim-sulfamethoxazole. This is the one that bothers me most, personally, when I'm tempted to take Bactrim if I'm going to Mexico.

—JOHN E. CONTE, Jr, MD

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Specialty Conference

Meningococcal Infections

Discussants
VICTOR K. WONG, MD; BETTY AGEE, MD; KWANG SIK KIM, MD; *and* HARRY T. WRIGHT, Jr, MD, MPH

An edited transcript of Medical Grand Rounds held at the Childrens Hospital of Los Angeles on March 6, 1987. Robert Adler, MD, Department of Pediatrics, is the coordinator of these conferences. This conference was edited by Victor K. Wong, MD, and Kwang Sik Kim, MD.

In Los Angeles, a substantial increase in the number of infections due to Neisseria meningitidis *has been noted. More alarming has been an associated mortality rate of 21%. The prompt recognition of meningococcal disease based on a high index of suspicion and the early institution of effective antibiotic treatment are essential for preventing complications and reducing mortality.*

(Wong VK, Agee B, Kim KS, et al: Meningococcal infections [Specialty Conference]. West J Med 1989 Jan; 150:68-73)

VICTOR K. WONG, MD*: Vieusseaux in Geneva first described "epidemic cerebrospinal fever" in 1805,[1] but it was not until 1887 that Weichselbaum in Vienna isolated the meningococcus from cerebrospinal fluid.[2] In 1898 Councilman and co-workers firmly established the etiologic agent of epidemic cerebrospinal meningitis when they found meningococcus in the cerebrospinal fluid of 31 of 34 cases.[3]

The possibility of a carrier state for meningococci was first proposed by Kiefer in 1896.[4] This was further documented in 1918 when Glover noted an increased carrier rate and incidence of meningococcal disease in military recruitment camps.[5]

Dopter in 1909 recognized that different serotypes of meningococcus existed.[6] He then began using serotherapy, which dramatically decreased the mortality rate from approximately 30% to 80% in untreated cases—and virtually 100% in infants—to less than 20%. This form of therapy was later replaced by the widespread use of sulfonamides in the 1940s for the infection itself as well as the carrier state. In 1963 clinically significant resistance to sulfonamides was recognized in outbreaks of meningococcal disease at two California military bases.[7,8]

Neisseria meningitidis is gram-negative and can appear as a single coccus or diplococcus. The flattened adjacent sides give the organism the typical "biscuit" or "kidney bean" shape when a fresh specimen is examined. It is important that laboratory processing be done rapidly because autolysis occurs with this organism. Although meningococci are not as nutritionally fastidious as gonococci, specimens from patients with possible meningococcal disease must be cultured on enriched media. If inoculated promptly, meningococci will grow on many different solid media such as blood agar, supplemented chocolate agar, or Mueller-Hinton agar. In addition, Thayer-Martin media can be used for oropharyngeal cultures. *Neisseria* species are fastidious in their growth conditions, and all media should be incubated at 35°C to 37°C under increased carbon dioxide content (3% to 10%) and humidity. The final identification of this organism is confirmed by a characteristic carbohydrate fermentation pattern—dextrose-positive, maltose-positive, and sucrose-negative—and being oxidase-positive or by direct latex agglutination testing.

The meningococcus produces a capsular polysaccharide that is the basis of classifying this organism into 13 different serogroups. The serogroups A, B, C, X, Y, Z, 29-E, W-135, and a newly described serogroup, L, have well-characterized capsular polysaccharides.[9] The capsular polysaccharides of serogroups D, H, I, and K have not been fully characterized.

The meningococcus may possess the ability to develop pili, which can enhance attachment to pharyngeal cells of the host.[10] This ability may influence the epidemiology and pathogenicity of this organism.

The importance of a bactericidal antibody and an intact complement system in protecting a host from meningococcal infection is well documented. Goldschneider and associates have shown that in persons with exposure to the organism who lack a serum bactericidal antibody to the infecting strain, there is a 30% to 50% chance of meningococcal disease developing.[11,12] This lytic antibody is directed primarily against the capsular polysaccharide and forms the basis for the development of potentially effective vaccines. In addition, lytic antibody has been found to be directed against noncapsular antigens, accounting for most of the "natural immunity" to meningococcal disease.[12,13]

Epidemiology

BETTY AGEE, MD*: Meningococcal disease occurs worldwide in endemic and epidemic forms. Attack rates during epidemics can exceed 100 cases per 100,000 population.[14] Most epidemics are caused by group A organisms, although epidemics of serogroup B and C disease occasionally arise.[15] The endemic rate of meningococcal disease in the United States over the past 40 years has varied from 1 to 3 per

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100,000.[16] Case rates fell in California during the 1970s after the military began routine vaccination.[17] Meningococcal disease in the US peaks in the winter-spring season. Age-specific attack rates decrease with age. Most cases occur in children younger than 5 years, and slightly more males than females are affected. In addition, overcrowding and poor living conditions predispose persons to meningococcal infection and disease. Contacts of patients with meningococcal infections who sleep and eat in the same household have a significantly increased risk of the disease developing compared with the general population, and they must receive chemoprophylaxis.

Since December 1986, Los Angeles County has experienced a substantial increase in the number of cases of meningococcal disease.[18] From December 1, 1986, through February 1987, there were 123 cases of meningococcal meningitis and meningococcemia reported compared with 37 cases for a similar period a year previously (Figure 1). The highest number of cases (68) was reported in January 1987. While the rate of meningococcal disease in Los Angeles County in the winter of 1986-1987 (1.5 per 100,000) is severalfold higher than that in the winter season in recent years, this year's rate represents a relatively small increase above baseline incidence when compared with meningococcal disease rates over many years.* Epidemic meningococcal disease last occurred in the United States in 1945 when the attack rate approached 14 per 100,000.[16] The introduction of an active surveillance of meningitis and bacteremia in Los Angeles County in January 1986 only partially explains the increased number of cases of meningococcal infection.

In the Los Angeles outbreak, 63% of the cases were in children younger than 5 years. Although these outbreaks have been sporadic, they have occurred throughout the entire county. As in the past, those districts with crowded conditions and a lower socioeconomic status have higher rates of disease. No secondary cases have been reported. The overall mortality rate of meningococcal disease cases in the Los Angeles outbreak, however, is 21%. (The statistics for this presentation were calculated by Nancy Bendana, PHN, MS, of the Los Angeles County Health Department.)

Since 1985 the proportion of serogroup C *N meningitidis* organisms has been increasing in Los Angeles while the proportion of serogroup B organisms, which have predominated for a decade, has decreased. Recently 77% of the organisms were serogroup C. Antibiotic sensitivity testing in 1986 indicates that all circulating *N meningitidis* strains are resistant to sulfadiazine but sensitive to rifampin.

Clinical Manifestations

Dr Wong: The spectrum of diseases caused by *N meningitidis* is diverse (Table 1). The diagnosis of meningococcal disease can be difficult to make at times as the spectrum of disease includes unsuspected bacteremia, pharyngitis, conjunctivitis, urethritis, pericarditis, primary arthritis, endophthalmitis, and fulminant sepsis with purpura fulminans. There also exists a low-grade chronic infection by *N meningitidis,* contrasted with fulminant meningococcemia that can result in death in a matter of hours.

Unsuspected meningococcal bacteremia represents one end of the spectrum of disease caused by *N meningitidis.* Patients with this disease can present with fever, nonspecific symptoms of an upper respiratory tract infection, arthralgias, otitis media, or a maculopapular rash. They are often sent home on an oral antibiotic regimen or no medication therapy. A blood culture may later reveal meningococcal bacteremia. In a review of 536 cases of bacteremia at Boston City Hospital, 26 cases of *N meningitidis* were found.[19] Of 25 cases available for chart review, 13 (52%) patients were considered sufficiently ill on an initial examination to require hospital admission. The other 12 (48%) patients were allowed to return home with a diagnosis of otitis media (6), pneumonia (2), fever (1), upper respiratory tract infection (2), or acute gastroenteritis (1). Eight patients received oral antibiotics and four patients received none. Three cases of meningitis were found on follow-up examination (two from the "treated" group), and two fatalities (both from the "untreated" group) resulted. Although it could not be concluded that orally administered antibiotics would have prevented the deaths of these two patients, reviewing the peripheral leukocyte counts on these patients did show neutropenia on the initial examination—less than 5,000 per μl. Thus, it behooves clinicians to maintain a high index of suspicion for the possibility of meningococcal infection in children with fever, especially if petechiae are noted on a physical examination or relative neutropenia is present.

Chronic meningococcemia was first described in 1902 by Solomon.[20] Since then, 150 to 160 cases have been reported.[21,22] Approximately 10% of these reported cases have been in patients younger than 16 years. The classic definition of chronic meningococcemia by Dock is "only those cases of

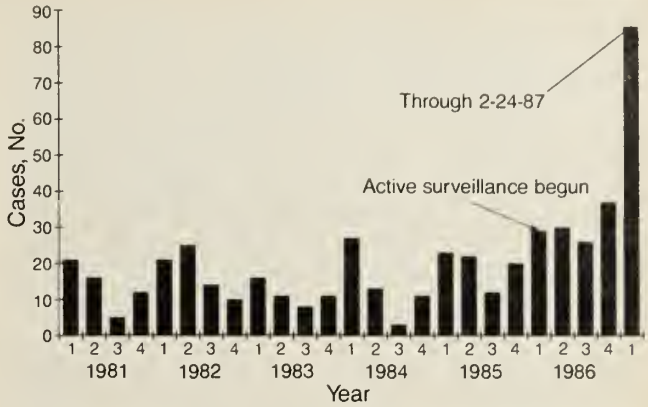

Figure 1.—The graph shows the number of meningococcal disease cases in Los Angeles County by quarter of onset, 1981 through February 24, 1987.

TABLE 1.—*Clinical Manifestations of Meningococcal Disease*

Asymptomatic	Oropharyngeal colonization
Minimal symptoms	Pharyngitis, urethritis, vaginitis, conjunctivitis, sinusitis
Bacteremia, acute	Primary arthritis, pericarditis, endophthalmitis, pneumonia, peritonitis
Bacteremia, chronic	Chronic meningococcemia
Septicemia with or without meningitis	Acute meningococcemia, fulminant meningococcemia (Waterhouse-Friderichsen syndrome)
Meningitis with or without meningococcemia	Meningococcal meningitis

*Los Angeles County continues to experience an increased incidence of meningococcal disease with 309 cases (17% fatality rate) reported in 1987 and 90 cases reported in the first two months of 1988.

meningococcemia in which there is a febrile period of at least one week without meningeal symptoms, and whose clinical course changed abruptly if meningitis supervened."[23] This clinical disorder is associated with intermittent or sustained fevers, headache, recurring rash (petechial or maculopapular), and various joint manifestations (arthritis or arthralgias). Benoit noted complications such as carditis, nephritis, and epididymitis in a third of 148 cases of chronic meningococcemia.[20] Identifying *N meningitidis* in a blood culture is the sine qua non in making the diagnosis.

Skin manifestations are the hallmark of meningococcal sepsis. Meningococcemia classically presents with a petechial rash although macular, maculopapular, and vesicular rashes have all been noted. Not uncommonly, patients may present with purpura fulminans and septic shock.

The time at which the rash appears, as well as the character, location, and distribution, may have prognostic significance. Stiehm and Damrosch reviewed cases of meningococcal infections in New York and found that the appearance of petechiae within 12 hours before admission was associated with a poor outcome.[24] Toews and Bass in Honolulu found that those patients with no skin lesions or those with generalized macular or petechial lesions had a less fulminant course.[25] In contrast, those patients with peripherally located purpuric or ecchymotic skin lesions had a high incidence of fulminant disease.

In addition to the dramatic dermatologic manifestations of meningococcemia, profound physiologic disturbances occur in the severe forms of meningococcal disease. Overwhelming sepsis accompanied by disseminated intravascular coagulation (DIC), adrenal damage such as Waterhouse-Friderichsen syndrome (hemorrhagic necrosis of the adrenal glands), bilateral renal cortical necrosis, and cardiovascular collapse can occur. The exact pathophysiology of shock in patients with acute meningococcemia is unknown. Myocarditis and myocardial dysfunction with a decreased left ventricular shortening fraction have been recorded by echocardiography.[26] Experimental data indicate that in severe meningococcemia with shock, the total volume of blood in the circulation remains unchanged.[27] The venous return to the heart is diminished, however, because of pooling of blood in the liver and mesenteric vessels, possibly due to generalized vasoconstriction of the hepatic veins. Although controversial, it appears that adrenal insufficiency is not the basis of shock in these patients; rather, it may be related to acute endotoxemia or a generalized Shwartzman reaction with resultant cardiovascular changes (vasomotor disturbance).

It has been noted that patients who have meningococcal sepsis without meningitis are more likely to have a fulminant course.[24,25] Other features associated with a poor prognosis include the presence of shock, a relatively low leukocyte count and erythrocyte sedimentation rate, myocardial dysfunction, and coagulopathy.

Management

KWANG SIK KIM, MD*: The optimal management of patients with meningococcal infections, particularly those with serious complications such as shock and DIC, is controversial.

Basically, the goal in managing meningococcal infections is to prevent serious complications and their sequelae. These complications can be divided into early and late (Table 2). Early complications usually accompany fulminant cases of meningococcal infection and include shock, DIC and thrombosis (such as purpura fulminans), heart failure due to myocarditis or myocardial dysfunction, and cerebral edema in the absence of meningitis. Late complications appear to be immunologically mediated—such as arthritis, pericarditis, and vasculitis—and occur more frequently in adults than in children. Long bone deformities may result from abnormal epiphyseal fusion in addition to complications of meningitis such as cranial nerve dysfunction. Thus, the optimal management of meningococcal infections will require differentiating those patients in whom serious complications are most likely to develop and to arrange for appropriate medical monitoring and therapy.

TABLE 2.—*Complications of Meningococcal Infections*

Early Complications
Shock
Disseminated intravascular coagulation, purpura fulminans
Heart failure due to myocarditis or myocardial dysfunction
Cerebral edema
Late Complications
Arthritis
Pericarditis
Vasculitis
Long bone deformities
Complications of meningitis, such as cranial nerve dysfunction

The most important element in managing patients with meningococcal infections is the early institution of effective antibiotic therapy. It should be noted, however, that clinical features of overwhelming infections due to other bacteria such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae* can mimic those of acute meningococcemia.[28,29] Gram's staining of cerebrospinal fluid, skin scrapings from purpuric or petechial lesions, and buffy-coat smears may help in identifying *N meningitidis.* In general, the initial antibiotic regimen should include agents active against *H influenzae* type b and *S pneumoniae* as well as *N meningitidis.* A combination of penicillin, usually ampicillin, plus chloramphenicol is commonly used, but this regimen has some theoretic and practical drawbacks in the treatment of patients with meningococcemia. First, a potential antagonism by the combination of ampicillin and chloramphenicol has been shown in vitro against *N meningitidis,* although such antagonistic effect has not been documented in vivo. Second, chloramphenicol has the potential to be toxic. Because chloramphenicol succinate is metabolized through the liver, any conditions interfering with hepatic function may result in toxic concentrations of chloramphenicol. There are several case reports of patients initially seen with meningococcemia and shock who later died of cardiovascular collapse (the gray baby syndrome).[24] Thus, chloramphenicol should be used cautiously in cases of meningococcemia, particularly in patients in whom early complications such as shock are most likely to develop.

A safe alternative in the presence of hepatic dysfunction or shock may be the "third-generation" cephalosporins such as cefotaxime sodium, ceftazidime, or ceftriaxone sodium. These cephalosporins are bactericidal in vitro against common childhood meningitis pathogens including *N meningitidis,* and their efficacy appears to be similar to that of

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ampicillin and chloramphenicol. Clinical experience with these newer agents, however, is limited.

Children with meningococcemia who are not critically ill when they are admitted to hospital may show rapid deterioration after antibiotic therapy is initiated. It has been suggested that antibiotic therapy may promote the liberation of large amounts of endotoxin and subsequently trigger a generalized Shwartzman reaction. Although this is theoretically possible—a similar phenomenon has been noted in patients with brucellosis[30,31]—there are no controlled clinical studies or experimental evidence to support this concept in humans with meningococcemia.

Controversy also exists concerning the use of heparin in the management of DIC and septic shock.[32,33] The rationale behind the use of heparin in patients with DIC appears to be twofold: first, heparin is a known anticoagulant, and, second, heparin is known to be effective in inhibiting the Shwartzman phenomenon and preventing fibrinogen deposition.[34] Thus, it appears that using heparin may be justified in those patients who present with purpura fulminans in addition to DIC. Unfortunately, there have been case reports of patients harmed by the inappropriate treatment of DIC with heparin.

Additional therapeutic modalities such as exchange transfusion, plasmapheresis, and leukapheresis are theoretically attractive,[35-37] but information based on controlled studies is lacking and, at present, their use in cases of meningococcemia remains experimental. Similarly, meningococcal antiserum and naloxone hydrochloride have been used successfully in a few cases of fulminant meningococcemia.[38,39] These limited experiences warrant further evaluation and at present remain experimental.

The most controversial issue in the management of meningococcemia with shock is the use of steroids. There are at least three different postulated mechanisms leading to septic shock that may be triggered by bacteria or their toxins. Release of adrenocorticotropic hormone and endorphin, activation of the coagulation system presumably through the Shwartzman reaction, and complement system activation primarily through C3a and C5a have been postulated.[40] Steroids have many theoretic benefits in controlling these three different pathways that can lead to septic shock. For example, steroids given early in the course of severe sepsis would be expected to suppress endorphin output and possibly reduce vasodilation. They also impair the activation of the alternative complement pathway, although its mechanism is unknown. Steroids in addition inhibit many activators of granulocyte function, stabilize lysosomal membranes, reduce histamine release, and inhibit prostaglandin synthesis by blocking the incorporation of membrane phospholipid into arachidonic acid. Thus, based on these theoretic benefits, high doses of steroids, particularly short-acting ones, used early in the course of severe shock might reduce adverse physiologic processes in cases of severe meningococcemia.

The decision of who should receive steroid therapy, however, is a difficult one because steroid therapy may be beneficial only to those subgroups of patients who will progress to end-organ failure or overt septic shock. In this respect, it would be helpful to have objective laboratory assays available to guide us in identifying patients at high risk of having malignant septic shock. As discussed earlier, several clinical and laboratory features in patients with meningococcal infection have been associated with an ominous prognosis (Table 3).[24,25,41,42] The use of steroids even in this subset of patients has not been definitively shown to be beneficial, and concerns over detrimental effects remain.

TABLE 3.—*Unfavorable Prognostic Features in Meningococcal Infection*

Petechiae present for less than 12 hours before admission
Purpura fulminans
Shock
No meningitis
Normal or low leukocyte count
Normal or low erythrocyte sedimentation rate
High fever—>40°C (104°F)
Myocardial dysfunction

Finally, the other important element of management is supportive care—that is, to prevent or to minimize hemodynamic and metabolic alterations.

Prevention and Prophylaxis

HARRY T. WRIGHT, JR, MD, MPH*: Each year 3,000 to 4,000 cases of meningococcal meningitis occur in this country. Among intimate contacts of patients with invasive meningococcal disease, the rate of a secondary attack within 30 days is 1% to 5%.[43] This figure exceeds the expected annual incidence in the general population by 1,000-fold. Therefore, preventing the disease is an appropriate approach.[44] Chemoprophylaxis using either rifampin or minocycline hydrochloride has been recommended; sulfonamides may be used if the infecting strain is known to be susceptible. Currently, the rate of resistance to sulfonamides is about 33% for group A, 14% for group B, and 75% for group C. A polysaccharide vaccine against disease caused by *N meningitidis* serogroups A, C, Y, and W-135 is currently licensed in the US. The vaccine consists of 50 μg of the respective purified bacterial capsular polysaccharides.[45] The serogroup A polysaccharide induces antibody in some children as young as 3 months, although a response comparable to that seen in adults is not achieved until 4 or 5 years of age; the serogroup C component does not induce a reliable antibody response before 2 years of age. A booster response after a second dose occurs with group A vaccine but not with group C vaccine.[46] Serogroup A vaccine has been shown to have a protective efficacy of 85% to 95% and to be useful in controlling epidemics. A similar level of clinical efficacy has been shown for the serogroup C vaccine. The groups Y and W-135 polysaccharides have been shown to be safe and immunogenic in adults and in children older than 2 years.[45] Antibodies against the group A and C polysaccharides decline substantially over the first three years following a single dose of vaccine. This antibody decline is more rapid in infants and young children than in adults.

Except for the military population, routine vaccination with a meningococcal polysaccharide vaccine is not recommended because the risk of infection in the United States is low; a vaccine against serogroup B, the major cause of meningococcal disease in the United States, is not yet available; and much of the meningococcal disease in the US occurs among children too young to respond to the current vaccines. In an outbreak of meningococcal disease, however, the serogroup should be identified and the population at risk determined. Older children, adolescents, and young adults at high

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risk may warrant vaccination if the outbreak is caused by one of the serogroups included in the vaccine.[45]

Routine immunization with the quadrivalent vaccine—groups A, C, Y, and W-135—may be indicated for certain immunodeficient patients at high risk for meningococcal disease, such as patients with specific complement deficiencies and anatomic or functional asplenia, although clinical efficacy has not been documented. The use of the vaccine should be considered to control outbreaks of disease caused by serogroups represented in the vaccine, and its use may be of benefit to travelers to countries recognized as having hyperendemic or epidemic disease as well as to Americans living in epidemic areas who will have prolonged contact with the local populace.[45] Pregnant women, however, should not be immunized unless there is a substantial risk of infection. The vaccine is currently given to all American military recruits.

For both adults and children, vaccine is administered subcutaneously as a single 0.5-ml dose. The vaccine can be given at the same time as other immunizations. Good antibody levels are achieved within 10 to 14 days. Specific immunity occurs from a single dose in 89% to 100% of vaccinations.[43] The duration of immunity is not known, and the need for booster doses remains to be determined, but revaccination after two or three years may be indicated for persons at high risk of infection, particularly children who were first immunized before 4 years of age. The meningococcal vaccines appear to be safe; localized erythema may occur and last one to two days, but no serious adverse effects are known.

Antimicrobial chemoprophylaxis of intimate contacts remains the primary preventive measure in sporadic cases of *N meningitidis* disease in this country because as many as half of the secondary cases of meningococcal infection occur after five days.

Unless the causative agent is known to be sensitive to sulfadiazine, the drug of choice for chemoprophylaxis is rifampin given twice a day for two days. The recommended protocol would be as follows: 600 mg every 12 hours for adults, 10 mg per kg body weight every 12 hours for children 1 month of age or older, and 5 mg per kg every 12 hours for children younger than 1 month. The sulfisoxazole dose is as follows: 1 gram every 12 hours for adults and children older than 12 years, 500 mg every 12 hours for children 1 to 12 years of age, and 500 mg daily for infants 6 months to 1 year of age.[47] There are no adequate and well-controlled studies of rifampin or sulfisoxazole prophylaxis in pregnant women. Teratogenicity studies in rodents suggest that both drugs may be associated with skeletal defects and abnormalities. The possible teratogenic potential in pregnant women should be carefully weighed against the benefits of prophylactic therapy with these drugs.

Household, day-care center, and nursery school contacts should receive antibiotic prophylaxis as soon as possible, preferably within 24 hours of the diagnosis of the primary case. Chemoprophylaxis is not routinely recommended for medical personnel except for those with intimate exposure, such as mouth-to-mouth resuscitation, before antibiotic therapy was begun.

Systemic antimicrobial therapy for meningococcal disease does not reliably eradicate nasopharyngeal carriage of *N meningitidis*. In a recent study, cultures of the upper respiratory tract in 28.6% of children were positive a week after completing intravenous ceftriaxone therapy for meningococcal disease.[48] Therefore, it is important to give chemoprophylaxis to an index patient before discharge from the hospital.

Conclusion

DR WONG: *Neisseria meningitidis* remains a significant cause of morbidity and mortality in Los Angeles County. A prompt recognition of early meningococcal infection in a child may prevent the complications of this potentially life-threatening disease. Meningococcal disease should be looked for in any child presenting with an acute occurrence of fever and associated rash. Early diagnostic procedures should include a complete leukocyte count, a blood culture, Gram's stain and culture of skin lesions (especially petechiae), and possibly a spinal fluid evaluation. Instituting empiric intravenous antibiotic therapy early is warranted in any child with possible meningococcemia.

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Determining Which Tests to Choose

IT IS PROBABLY BEST to individualize our decisions, perhaps view the issue of prevention as a set of basic interventions that every person should have and then a set of interventions that are in major part determined by risk factors. In primary prevention, the basic set for adults should always include immunizations, recommending smoking prevention or cessation, encouraging seat belt use in automobiles, and use of smoke detectors in the home. Such things as use of the hepatitis B vaccine may make sense for groups at risk.

In the case of secondary screening interventions, there may be a basic set that every adult should have. Although there is controversy about this, I think we can say that a breast examination, by the primary care giver and used as a way of teaching self-examination to a woman, probably makes sense. Even recognizing the controversy about repeat intervals, the Pap smear makes sense, as does a rectal examination. If one is doing a pelvic examination in order to do a Pap smear, the rectal examination as part of that has a small marginal cost. And in the case of men who are at risk for prostate cancer, we should use the screening test that we have, even recognizing that it is not a great screening test. Checking the blood pressure and detecting and treating hypertension probably make sense. Mammography, even recognizing the repetition controversy and differences in recommendations between yearly for women aged 50 to 59 versus 45 to 65, is a good idea. Cholesterol screening . . . I wish I knew. It may be effective as an educational tool, in young people particularly, as a way of providing a lever, a hook to get somebody to change their dietary habits. And if treatment comes along—and there has been some recent publicity about a new medication that is supposed to have much greater acceptability—available therapy may influence the appropriateness of cholesterol screening. Stool for occult blood—again, I wish it were a better test. It may make a great deal of sense in certain populations at risk. It is not a wonderful test. Compliance remains a problem. False positives remain an issue.

—GERALD CHARLES, MD

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Epitomes

Important Advances in Clinical Medicine

Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in plastic surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Treatment of Burned Hands

LIKE THE REST OF MODERN BURN TREATMENT, the care of burned hands has focused on early excision and grafting. I prefer to excise and skin graft deep partial-thickness wounds even at the risk of removing potentially viable tissue. This type of wound tends to produce hypertrophic scar and stiffness if allowed to heal by granulation and epithelialization. Determining the depth of an injury continues to require the experience and skill of a burn surgeon, although objectively measuring cutaneous blood flow with a laser Doppler is potentially useful.

Following the initial cleaning of a burn wound, the hand is elevated and splinted with the metacarpophalangeal joints flexed to 90 degrees and the fingers straight. The thumb is held in abduction. Superficial burns may be wrapped in protective occlusive dressings or gloves made from synthetic skin (Biobrane) applied. Deeper injuries are treated with topical antibacterials, usually silver sulfadiazine, and observed for several days until edema has resolved. With circumferential burns of the hands and forearms, the possible need for escharotomy to prevent vascular compression is evaluated clinically and by measuring tissue pressure with a wick catheter.

Hand burns that appear likely to epithelialize within two weeks are given a chance to heal on their own. Deeper wounds are excised and skin grafting done as soon as the patient is stable. A tangential excision that leaves the lower dermis is preferred when the burn has not damaged this layer, as it provides a stable base for the new skin grafts and prevents wounds from contracting. Enzymatic removal of the burn-injured outer dermis is an alternative method of preparing the wound for skin grafting and can even prevent the need for open escharotomies. Unexpanded meshed skin grafts are frequently used and give excellent functional results, but, unmeshed sheet grafts, while technically more exacting, give better cosmetic results.

Patients with newly healed hand burns and grafts frequently require intensive rehabilitation with supervised exercises, dynamic splints, and pressure garment gloves to prevent hypertrophic scar and stiffness. Many patients who in the past would have been left with severe contracture deformities and a future of many reconstructive operations can now realistically look forward to a fully functional and cosmetically acceptable hand after a burn injury.

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Functional Results After Microvascular Operations

MICROVASCULAR SURGICAL TECHNIQUES have become effective in reconstructing acute and chronic deformities. The overall success rate of replanted parts in most microsurgical centers is about 86%, with laceration type amputations having the lowest success rate (76%). The replant success rate falls off to 60% when the cold ischemia time of a replanted part is longer than 20 hours. The use of medicinal leeches *(Hirudo medicinalis)* has increased the survival of replanted crush-injured parts.

The functional results of digital replantation are encouraging. In a recent review of 142 replanted digits, 31% had excellent results, 54.9% had good results, 10.7% had fair results, and 3.5% had poor results. Results are based on range of motion, sensation, subjective symptoms, cosmesis, and patients' satisfaction.

Microvascular free tissue transplantation is now the method of choice to solve many difficult reconstructive problems. Coverage of the distal third of the tibia, as in grade 3 to 4 open tibia-fibular fractures, is best accomplished by free latissimus dorsi muscle transplantation. The transplanting of serratus anterior muscle or de-epithelialized skin flaps is now used extensively in reconstructing soft tissue deficits of the

face in patients with hemifacial atrophy (Romberg's disease), hemifacial microsomia, or in those who have had head and neck cancer resections. Near-symmetric movement in patients with facial paralysis is frequently attained following cross-facial nerve grafting and free serratus anterior muscle transplantation. The success rate of using free flaps averages 93% to 95% in most microsurgical centers.

Toe-to-hand transplantation is now being done on hundreds of patients with traumatic or congenital loss of digits. The transplanted toes function best when the great toe is used for thumb reconstruction and the second toe, from either one or both feet, is used for finger reconstruction. Sensation of the transplanted digit is close to normal: 10- to 20-mm two-point discrimination. Grip strength of transplanted toes is 60% to 80% of that of the uninjured side. In all, 95% of patients have no donor site morbidity and are able to resume their preinjury activity levels.

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Lipoplasty

LIPOPLASTY, or liposuction, has had a profound effect on the practice of plastic surgery, becoming in just five years the most common aesthetic procedure done in the United States.

The techniques used in lipoplasty are conceptually contrary to those used in traditional operations. Surgeons typically work through open incisions, excising tissue with sharp instruments while directly viewing their field of work. A lipoplasty surgeon makes only a small incision through which a blunt cannula, attached to high-powered suction, is passed into the subcutaneous fat. The cannula is moved back and forth in the subcutaneous fat while the tissue is molded with the opposite hand; during this procedure the surgeon is unable to see the tissue directly.

Yves-Gerard Illouz is the originator of the technique of lipoplasty. Using a blunt instrument preserves the fibrous septa, which contain the blood vessels and nerves, coursing vertically in the subcutaneous fat from the deep fascia to the underlying surface of the skin. Preserving the septa allows the skin to collapse, avoiding a pocket that could lead to the accumulation of fluid and its related problems.

Since the introduction of lipoplasty to the United States five years ago, several modifications have been made. Epinephrine has been added to the preoperative wetting solution. A low-dose concentration, approximately 1:400,000, has been shown to reduce the amount of blood present in the fat aspirate by about 50%, thus allowing for the safe removal of greater volumes of fat.

Because of the need for good skin elasticity, it was initially thought that suitable candidates for lipoplasty must be younger than 45 years. Studies have subsequently shown that patients who have satisfactory skin elasticity in their fifth, sixth, or seventh decade make good candidates for lipoplasty, both physiologically and psychologically. Older patients are often better candidates psychologically than younger ones.

Lipoplasty was originally designed for removing accumulations of fat in the torso and lower extremities. More recently it has been effectively used in other sites, specifically the head and neck, and for reconstructive procedures such as the removal of solitary or multiple lipomas and the debulking of flaps. Gratifying results have been attained particularly in the neck in the use of both closed aspirative lipoplasty and lipoplasty combined with rhytidectomy. Interest in its use at other sites such as the knees, calves, and ankles is increasing.

Problems have occurred with the procedure, the more horrific of which have received national publicity. These appear to be related to the removal of too much fat, the occurrence of infection, or the sequelae of contouring defects. These problems can be reduced with limited fat removal, a proper sterile technique, and well-trained surgeons. Studies indicate that, in qualified hands, the incidence of complication is low.

We now have a safe and effective method of removing subcutaneous fat. Currently used primarily for removing localized fat, the ramifications of the technique have not yet been fully examined. In addition to its effect on plastic surgery, lipoplasty may affect other aspects of the practice of medicine.

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Peripheral Nerve Repair and Regeneration

THE MANY COMPLEX ISSUES surrounding the ideal methods of treating peripheral nerve injuries continue to be a focus of divergent opinions. During the past decade, however, surgeons have generally agreed on the usefulness of thin peripheral nerve grafts for nerve deficits too great to be overcome by approximating proximal and distal stumps by more than modest tension. Also, there is growing consensus that repair techniques that enable surgeons to better match fascicles or groups of fascicles enhance ultimate functional recovery, though a definitive study clearly showing this has not been done.

While fascicular matching techniques and nerve grafting have helped to solve some difficult clinical problems, many remain. Recently, intensive research has led to several new advances toward possibly solving these difficult remaining problems such as severe injuries to the brachial plexus where long gaps between proximal and distal nerve stumps exist.

Laboratory studies have indicated that nerve axonal regeneration across a vascularized nerve graft—a nerve graft that is harvested with its accompanying artery and vein, which can then be sutured by microvascular anastomotic techniques to a recipient artery and vein, providing an ongoing blood supply to the nerve graft segment—may be better than that across standard nerve grafts.

Human anatomic studies have identified several expendable nerves that accompany expendable arteries and veins of a size suitable for microvascular anastomosis. These include the sural nerve, antebrachial cutaneous nerve, radial sensory nerve, and the distal peroneal nerve. In selected clinical situations, for example, patients with long defects or defects that cross extremely scarred or hypovascular areas, the chances of ultimate functional recovery may be improved.

Recent intensive research into sutureless repair methods has led to the concept of using artificial nerve conduits in place of nerve autografts to overcome deficits of a modest length. Laboratory studies using both rats and nonhuman primates showed that regeneration through a biodegradable nerve conduit was equal to that across standard nerve grafts. The advantage of such a technique, obviating the need to harvest an autograft from a donor site with the potential creation of a painful neuroma, is obvious.

Finally, as experience with tissue expanders grows, surgeons are finding that peripheral nerves can be gradually lengthened by tissue expansion techniques. Laboratory studies indicate that the lengthened segment maintains anatomic and physiologic continuity. By lengthening the distal (denervated) segment, significant nerve gaps might be overcome.

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Gynecomastia

GYNECOMASTIA (Greek *gynec,* denoting "relationship to women," and *mastos,* "breast") refers to the presence of femalelike mammary glands in a man or a boy. An incidence as high as 65% in adolescents and 40% in adults has been reported. Most patients are not treated. Adolescents are usually told they will outgrow the problem, and most adults either are told to lose weight or are not sufficiently bothered by its presence to seek treatment.

Considering the high incidence of gynecomastia and the fact that medical treatment is rarely indicated and more likely is contraindicated, surgical treatment should be considered in properly selected patients. Surgical correction is particularly important to counter the self-consciousness and embarrassment that invariably accompany this disorder in adolescence.

Numerous conditions may be associated with gynecomastia. They may be categorized as physiologic (neonatal, pubertal, or involutional), endogenous (testicular, adrenal, thyroid, pituitary, or other), or exogenous (hormones or drugs). In most patients a cause cannot be identified. If it develops slowly and is asymptomatic, the cause may be ignored in an otherwise healthy person. If the gynecomastia began before puberty, the cause should be investigated. When it begins during puberty, the cause is usually idiopathic. Because 62% of cases of gynecomastia may be drug related, a drug history may be helpful. It should be noted that the extent of gynecomastia of any cause may be greatly asymmetric or even unilateral.

Although carcinoma of the male breast is rare, accounting for 0.2% of all cases of carcinoma in men, should a unilateral, firm, irregular mass be detected on examination, a biopsy should be done. Otherwise, biopsy is unnecessary.

The surgical technique must be adapted to the size and type of gynecomastia and the amount of redundant skin. Whenever possible, the incisions should be done at the border or within the areola without displacing the nipple. Historically, surgical treatment consisted of sharp dissection of the fat and parenchymal tissue that make up the deformity. Undesired sequelae and complications included unattractive scars, contour deformities, and hematoma. Since 1980 many plastic surgeons have been using suction lipectomy as well as sharp dissection in the treatment of gynecomastia. With the addition of suction lipectomy, the incidence of contour deformities and hematomas has decreased. Some patients can be treated with suction lipectomy alone, but most require a combination approach. Suction lipectomy is done first, followed by sharp dissection of any residual parenchyma that requires removal. In general, excellent cosmetic results can be expected from experienced plastic surgeons.

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Head and Neck Reconstruction

TUMOR ABLATION in the head and neck area has a major functional and aesthetic impact, causing profound changes in the subsequent quality of life. This is especially the case if reconstruction is delayed for fear of masking recurrent disease. This concept is now untenable as computed tomographic (CT) scans and CT-directed needle aspiration biopsies are reliable in detecting disease, even in deep tissues. Further, immediate reconstruction offers the best chance for early rehabilitation. The goals of such reconstruction are to restore speech and swallowing, prevent aspiration and drooling, and produce a primarily healed wound with the least possible deformity.

Two advances in the past ten years have dramatically altered our approach to this problem. McCraw's description of independent myocutaneous vascular territories in 1977 led to the definition of several useful myocutaneous flaps for a head and neck operation. The pectoralis major myocutaneous flap

is the most versatile one, offering a large skin paddle for oropharyngeal or cutaneous replacement and a bulky muscle that can securely cover irradiated carotid vessels. The trapezius and latissimus dorsi myocutaneous flaps have also been used for similar purposes. These single-stage reliable flaps have now replaced temporal, deltopectoral, and multistage tube pedicle flaps.

The second major advance has been in describing fasciocutaneous and compound flaps suitable for microvascular transfer to the head and neck. The radial forearm and parascapular fasciocutaneous flaps have the advantage of thinness and conform well to a three-dimensional defect in the oral cavity and oropharynx. The tethering effect of a bulky myocutaneous flap on the tongue is avoided, thereby enabling better speech and swallowing. The iliac osteocutaneous free flap can be used for immediate, one-stage total mandibular reconstruction, even in previously irradiated fields, eliminating the "Andy Gump" deformity. Replacing the pharyngoesophagus with a revascularized segment of jejunum allows for early swallowing and adequate oral intake as early as one week after the operation. Microvascular reconstruction offers the distinct advantages of functional tissue transfer and a superior aesthetic result. The risk of complete failure due to vascular thrombosis is ever present, however. Microvascular expertise and considerable experience are critical factors for a successful outcome.

It is clear that one-stage immediate reconstruction for head and neck cancer improves the quality of life and shortens the hospital stay. This is especially important when a cure is uncertain and life expectancy is limited.

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Flap Surgery in the 1980s

IN RECENT YEARS there has been a concentrated national and international effort directed at reexamining the blood supply to the skin. As a direct result of this intensive effort, the number and versatility of available flaps have grown dramatically over the past few years. This has resulted in an ability to treat the most complex injuries and defects. The blood supply to skin, and therefore flaps, has been divided into four basic groups. First, "random flaps" have a blood supply that is entirely dependent on a subdermal vascular network, or plexus. Beneath this plexus, running on the surface of the deep fascia over the muscle, is another vascular network that communicates with the subdermal plexus through a series of vertical vessels in the subcutaneous tissue.

The elevation of a flap incorporating the deep fascia, the subcutaneous fat, and vessels including the skin is the second group, referred to as a "fasciocutaneous flap," and elevation of the flap, including all of the above with the underlying muscle, is the third, known as a "myocutaneous flap." Perforating vessels running directly from the muscle to the skin through the two previously mentioned plexuses are responsible for this relative revolution that has occurred in reconstructive plastic surgery. As experience has shown, not only do we have "spare" or expendable muscles available, but the large size of muscles such as the latissimus dorsi muscle or the skin territory supplied by the rectus abdominis muscle, among others, has allowed for the reconstruction or coverage of large defects of complex structures such as the breast after a mastectomy.

Recently it has become evident that the vascular plexus over the fascia may be fed not only from perforators arising from the underlying muscle but also by direct communication from deeper, well-known vessels such as the radial artery or the peroneal artery in the leg, which is the fourth type of blood supply.

The selection of a flap based on these larger vascular pedicles has dramatically improved the versatility and safety of these flaps in reconstructing areas as diverse as the hand and the head and neck. The added ability to include viable bone or even nerves has dramatically increased the range of reconstruction options available. Our improved understanding of the blood supply to skin and underlying structures has now made it possible to reconstruct defects safely in one stage with far less disfigurement to patients and with functional results that, even if possible, were far more complex to achieve just a few years ago.

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Tissue Expansion

TISSUE EXPANSION was introduced to the plastic and reconstructive surgery community in 1976 as an alternative method for providing ideal and additional local tissue cover. Improved techniques have resulted in shorter hospital stays, decreased morbidity and complication rates, and stable aesthetic and functional reconstructions. In addition, advances in implant design and concepts now permit clinicians to vary their reconstructive procedures by using the expansion technique.

Long-term expansion is a procedure whose end result is similar to the effects on the anterior abdominal wall produced by the enlarging uterus in a pregnant woman. Long-term expansion consists of two stages: first, the expander(s) is inserted; and, second, expanded tissues advance after a period of serial expansions for as long as two to four months. The newly recruited skin may provide near-perfect color, texture, and sensory qualities to match the lost skin. The hallmark of the procedure remains a minimal donor-site scar. At this time, the source(s) for the additional tissue remains

unclear but can be attributed to a direct stretching of skin, an inward migration of tissue, or the stimulation of cells to divide and multiply.

Intraoperative expansion is a new technique to stretch tissues during the surgical procedure. The amount of tissue stretched depends on its pliability and extensibility. These characteristics are in part determined by the intrinsic thickness and elasticity of dermis (location, genetic factors, and patient's age) and acquired changes in the characteristics of the tissues (scar, irradiation, and inflammatory changes). Intraoperative expansion differs from long-term expansion by offering the following inherent advantages that reduce the duration of expansion: the absence of a retained, buried foreign body; the absence of a physical deformity, especially in the head and neck areas; and the immediate availability of tissue for reconstruction. The technique most aptly applies to the coverage of small to medium-sized rather than of larger defects.

Directional expansion is possible with the development of expanders that stretch more in one area than another. Thus, during long-term expansion, more tissue may be recruited in a preferred location by the directional bulge of the expander. Directional expansion is currently applied to improve the results of scalp expansion and breast reconstruction.

A tissue expander has been developed that, once inflated to an appropriate size, is left in position as a prosthesis. The remote valve and tubing are withdrawn from the expander under local anesthesia, eliminating the need for a second procedure. The most rapid acceptance of this type of permanent expander has been in the area of breast reconstruction.

Complications have been substantially reduced over the past ten years because of improved patient selection, technique, and surgeon education. An exposure of expander units to contamination and infection has been the major complication of this technique.

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Three-Dimensional Imaging in Surgery

THREE-DIMENSIONAL IMAGING is a newly established imaging modality based on computed tomographic (CT) and magnetic resonance imaging data. The modality is the result of computer processing of the scan data on a slice-by-slice basis. Using various algorithms, the edges of interest are detected and specific tissues selected for display. These processed cuts are then stacked, interpolated, and shaded to provide a three-dimensional view of the anatomic area of interest. The modality has been useful as an adjunct to diagnosis and surgical planning, with its usefulness extending to the specialties of neurosurgery; orthopedics; plastic and reconstructive surgery; oral surgery; ear, nose, and thoat surgery; orthognathic surgery; medical oncology; diagnostic radiology; and radiation therapy planning. Its application to areas of soft tissue analysis is rapidly growing.

The surgical usefulness of the data is enhanced by the ability to interact with the scans to provide cutaway and disarticulated views. Though no new data are added in the process, studies confirm a significant diagnostic advantage in three-dimensional imaging, especially evident in spinal disorders—vertebral and foraminal stenoses, fractures, spinal fusion assessment—pelvic trauma, and craniomaxillofacial problems.

The availability of the process depends on specialized software running either on a CT scanner computer or on one of several add-on image processors. Using scanner software has built-in limitations of appropriating CT scanner time (thus limiting the number of procedures requiring CT) and limited interactivity with the scan data. While usually somewhat more expensive, add-on processors usually process data from multiple scanner manufacturers and permit a full range of interactive two-dimensional and three-dimensional viewing, life-sized representations of data, on-screen metric capability, and volumetric analysis for tumor tracking.

The technology is further extended by the use of the data to drive a numerically controlled machine tool to provide solid, three-dimensional, hands-on models of the bony anatomy of interest for teaching, rehearsing surgical procedures, or designing implantable prostheses.

Third-party reimbursement has been established and requires the proper relative-value schedule coding.

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Congenital Nevi—Risk of Malignancy

THE INCIDENCE OF MALIGNANT LESIONS in congenital nevi has been estimated to be between 1% and 10%. Size, location, and histologic type seem to be factors. The larger the lesion, the higher the risk. Giant nevi—greater than 100 cm sq—may have an incidence of 5% to 10%. Small congenital nevi have not been adequately studied, but 40% to 60% of melanomas are associated with preexisting small nevi. It has not been established that these small nevi were congenital.

The most common sites for malignant degeneration in giant nevi are the posterior scalp, neck, back, and buttock; 80% of malignant lesions occur in these areas. There is a lower risk of malignancy in giant nevi of the face and extremities, but the reason for this differential risk is not known.

The most common age for a malignant lesion is during the first year of life. High risk is encountered also during early childhood, and then the risk is reduced during puberty and later life. Early excision is therefore indicated when feasible.

The treatment of choice is complete excision of a nevus through the level of the subcutaneous tissue, accompanied by

replacing the skin with either full-thickness skin grafts or flaps. The method of skin replacement and the sequencing of the excision are determined by the size and location of the lesion. Full-thickness skin grafts are used on various parts of the face. Whenever possible, the skin on the trunk and extremities is expanded subcutaneously with silicone inflatable prostheses. This method is ideal for giant nevi of the scalp. Dermaplaning with a mechanical dermatome, or dermabrasion, is used only as a compromise treatment because only the superficial half of the lesion is removed and the neval cells in the deep dermis and around hair follicles remain. The malignant potential of the residual nevus is not known. Although dermabrasion was initially advised only during infancy, it can be done at any age. The pigmentation is greatly reduced, but hair follicles remain.

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Editorials

Musings on the Election

As this is written the national election is just over and there will be a new administration, a new Congress, and many new state and local officials. This was a year for returning the incumbents to office. The Republicans remain in the White House, the Democrats remain in control of the Congress, and to a great extent the incumbents prevailed in the state governments. There may have been more change in local governments where purely local issues were more readily addressed by voters. Somehow the election, no doubt the envy of many less privileged societies in the world, leaves one with an uncomfortable feeling that this process somehow failed to meet our needs as a nation in today's world. At the national level, for example, some of the most important issues pertaining to our future as a competitive nation were hardly even mentioned, let alone discussed in any meaningful fashion, during the campaign. The voters were really not able to give much direction to their elected or re-elected officials. One has an uncomfortable sense that as a nation we seem to be drifting purposelessly, rather than seriously addressing problems that must be faced and dealt with if we are to compete successfully in what is so obviously an increasingly competitive world. This has to be a serious matter for our future, since there is reason enough to believe that we have already begun to lose ground to some of our existing and potential technologic, social, economic, and political competitors in the rest of the world.

Our system, as it has evolved, seems to consider the future about as far ahead as the next election in the public sector of government, or the next bottom line or stockholders' meeting in the private sector of business or industry. This is ingrained and not likely to change without some considerable external stimulus. If we are to give more attention to what might need to be done today to better prepare ourselves for the ever more intensely competitive future ahead, the initiative must come from somewhere. Hardly anything can be more important to the future of this nation and its citizens.

It is suggested that something is needed to focus attention and provide a sense of genuine national purpose. There is already a growing concern that we may have been giving little more than lip service to such things as basic health care for those who need it and do not have it, and education for all our citizens. Without doubt a healthy and educated citizenry is essential for any nation to compete well in the social, economic, and political world environment that lies ahead. Physicians naturally think in terms of health because health is what we are all about. Perhaps it is time for the nation to prepare for its future by making a national determination that ours must become a healthy nation in the fullest sense of the term. Health, as we have come to understand it, has many dimensions. It involves personal, public, and environmental health. These in turn require that there be social, economic, and political health, and it follows that a literate and educated citizenry is essential for each of the above. Ill health in any of these dimensions brings illness to patients, societies, and nations, and it is not to be forgotten that weakness accompanies ill health wherever it occurs.

Physicians are among the more educated of our citizens and also are among those more dedicated to health, whether this be personal, public, environmental, social, economic, or political, or dedication just to the degree of literacy and education that is necessary for health and health care. Should physicians, with perhaps a longer view than some of what is needed for a healthy future, sound a clarion call to persuade this nation to prepare more realistically for the future? If there is need for a national purpose, could this purpose be a determination to become a healthy nation in the broad sense that has been described? Such a national purpose would surely be one worthy of our destiny as a nation, and, if achieved, could only serve us well. But alas, like elsewhere in our democratic society, even in the medical profession and in medical associations, the future is more often addressed only in the short range, that is, from year to year, from one society election to the next. If this is to become a strong, healthy nation in the sense described herein, where lies the responsibility to bring this about, and how is this responsibility to be exercised?

MSMW

Meningococcal Infections—What's Next?

Serious meningococcal infections, primarily meningitis and sepsis, continue to be a major health problem in many parts of the world. Victor Wong, MD, elsewhere in this issue concludes that "*Neisseria meningitidis* remains a significant cause of morbidity and mortality in Los Angeles County." In Los Angeles County, the attack rate is 1 to 5 cases per 100,000 population per year. Yet, in Zaria, Nigeria, the rate of meningococcal meningitis is 63 cases per 100,000 population per year. In both locales meningococcal disease occurs primarily in children. Diseases caused by *N meningitidis* are a worldwide health problem.

Current and future work on preventing invasive meningococcal disease includes making the currently available quadrivalent vaccine (derived from capsular polysaccharides) highly immunogenic in very young children. Because newborn infants can produce antibodies to proteins (such as tetanus toxoid) but fail to produce antibodies to polysaccharide antigens, the approach is to covalently link the capsular carbohydrate (or a haptenic portion thereof) to a protein. The resultant antibody response to this conjugant vaccine is to both the protein and the carbohydrate. Pilot studies have shown that conjugant vaccines evoke high titers of anticapsular antibody. The presence of higher titers of anticapsular antibody correlates with protection from bacteremic infections—sepsis, meningitis, and arthritis, for example. Anticapsular antibodies have no effect on nasopharyngeal carriage, however. Thus, the spread of meningococci through a community would not be affected by such a vaccine.

A logical extension of the conjugant vaccine concept is to covalently link the capsular carbohydrate to a meningococcal surface protein whose antigenicity is conserved among all strains. Such a vaccine may not only be consistently immunogenic in all ages but would be directed against two bacterial structures—a one-two punch. If the meningococcal surface protein were necessary for colonization, person-to-person spread could also be prevented. Another approach to developing an antimeningococcal vaccine is to develop a surrogate image of the antigenic portion of the capsular poly-

saccharide. A mirror image of the capsular antigen is present in the combining site of an antibody directed against that haptenic portion of the capsular carbohydrate. When administered, the antibody acts as an antigen. One of the haptenic sites on the anticapsular antibody is this mirror image of the capsular hapten. Antibodies against this portion of the antibody—that is, anti-idiotypic antibodies—can confer protective immunity against the pathogen. This novel approach is being pursued with meningococci.[1] Thus, the future looks bright for meningococcal vaccines; the only problem, then, will be administering them to the population at risk.

An effective vaccine is urgently needed because the meningococcus is learning to escape penicillin action. In the first six months of 1986, 5% of meningococcal organisms isolated from blood or cerebrospinal fluid in Spain were relatively resistant to penicillin G—that is, the amount of antibiotic needed to inhibit bacterial growth increased fourfold.[2] The clinical outcome could not be correlated with antibiotic resistance, but no chances were taken: cefotaxime sodium is now administered for all suspected meningococcal infections in Spain. Although all Spanish strains are currently susceptible to cefotaxime, this antibiotic will probably not continue to be effective. The reason is that meningococci are evolving a penicillin-resistant mechanism similar to that which occurred in South African pneumococci. A mutation in one target of penicillin G of the meningococcus, called a penicillin-binding protein (PBP), decreases antibiotic affinity and activity.[3] Additional mutations in similar or identical targets further decrease the susceptibility to penicillin G and also decrease the susceptibility to related β-lactams: ampicillin, cephalothin, cefuroxime.[3] It is easy to envision yet another mutation in the PBP system resulting in cefotaxime resistance.

It also appears that the meningococcus has acquired the ability to produce β-lactamase by the acquisition of an R-plasmid.[4] If the meningococcus is at all like *Haemophilus influenzae,* invasive disease caused by such strains would not respond to penicillin (or ampicillin) administration; cefotaxime should be effective. Of greater importance is the likelihood of a β-lactamase-producing strain to acquire an additional gene (or genes) on the plasmid that encodes for other antibiotic-inactivating enzymes. Chloramphenicol and kanamycin acetyltransferase have coevolved with β-lactamase in invasive *H influenzae.* Virtually all such strains are also tetracycline-resistant. If this occurs in meningococci, then alternative non-β-lactam antibiotics (such as chloramphenicol) will not be an effective alternative. The "worst-case" scenario would be strains harboring all of the above antibiotic resistances and a cephalosporinase capable of degrading newer third-generation cephalosporins.

What about the next five years? We can no longer assume uniform susceptibility of meningococci to penicillin G. Antibiotic susceptibility testing of meningococci (currently not routine) will have to be instituted and antibiotic therapy based on the results. We will be able to count on the pharmaceutical industry keeping one step ahead: newer quinolines, such as ciprofloxacin, are active against the meningococci. It is hoped that a uniformly efficacious vaccine will be developed before the meningococcus gets ahead of the pharmaceutical industry.

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The Place for Vestibular Function Tests

In this issue of the journal, Baloh and Furman have presented a thorough, state-of-the-art review of laboratory tests of vestibular function. The crucial issue for practicing physicians is how to incorporate information supplied by vestibular laboratories into the clinical analysis of patients with dizziness, imbalance, or both. To accomplish this, clinicians must first clearly understand how the vestibular system functions in health.

The vestibular system acts through two phylogenetically old, posture-stabilizing reflexes—the vestibulo-ocular reflex and the vestibulospinal reflex. Sensory information for these reflexes is provided by the semicircular canals, which transduce angular acceleration and hence sense rotation of the head, and by the otolith organs (utricle and saccule), which transduce linear acceleration, including gravity, and hence sense the position of the head with respect to a vertical upright posture. The vestibulo-ocular reflex can use information from the semicircular canals to generate a compensatory rotation of the eyes (the slow phase of vestibular nystagmus). In this way, during rotation of the head we can keep steady on the fovea the image of objects that are stationary in the outside world. The vestibulo-ocular reflex allows us to move and to see at the same time. Information from the otoliths about the pull of gravity can also be used to generate another type of vestibulo-ocular reflex—counterrolling of the eyes when the head is tilted to the side. Vestibulospinal reflexes also use information from the semicircular canals and the otoliths to generate appropriate readjustments in body and limb tone to keep us upright and prevent us from falling.

Lesions in the vestibular system cause two main types of physiologic disturbances: static and dynamic. A static disturbance reflects an imbalance in the level of tonic activity in the vestibular nuclei. The difference is usually between the vestibular nuclei on either side of the brain stem and is manifest as a unidirectional spontaneous nystagmus and a tendency to fall or to lean in one direction. A dynamic disturbance reflects an inaccurate (dysmetric) response during head motion and is characterized by slow phases of induced vestibular nystagmus and postural readjustments of the body that have a magnitude or direction that is not commensurate with the magnitude or direction of the motion of the head.

With this background, let us examine critically the only vestibular function test that is readily available to most clinicians—the electronystagmogram or ENG, in which movements of the eyes are recorded electrically in the light and in the dark both before and during irrigations of the ears with hot and cold water. The ENG provides three major pieces of information: the presence or absence of spontaneous nystagmus, the presence or absence of nystagmus induced by a change in head position, and the nystagmus response to caloric irrigations. What do we do with this information?

Both spontaneous and positional nystagmus are important neurologic signs, but they can be more easily identified at the bedside than in the laboratory provided the ability of the patient to use visual fixation to suppress nystagmus is eliminated. This can be accomplished easily with Frenzel glasses (internally illuminated goggles containing high-magnification spectacle lenses). Frenzel glasses allow the examiner to see the eyes of the patient but prevent the patient from fixing on objects. Thus, by eliminating fixation, any inherent spontaneous vestibular nystagmus becomes manifest and can be detected by the examiner. It must be remembered that small amounts of spontaneous and especially positional nystagmus can be recorded with an ENG in many normal persons.

The response to caloric stimulation is a measure of dynamic vestibular function. It is probably the most useful information that can be gleaned from an ENG, with the following caveats:

- Caloric testing assesses the function of the lateral semicircular canals only—not of the vertical canals or the otolith organs.
- The range of values of the response to caloric irrigations in normal persons is wide both in amplitude and symmetry. Consequently, the caloric test is relatively insensitive to partial labyrinthine lesions.
- The caloric test is subject to technical problems, such as the presence of cerumen, that may cause difficulty in simultaneously delivering an equal quantity of water at the same rate and temperature to each ear. If such sources of artifact are not kept in mind, decreased vestibular function in one or both ears may be mistakenly inferred. Caloric testing must be carried out by experienced personnel paying rigorous attention to careful technique.
- Caloric irrigations mimic a head rotation that is composed only of low frequencies. Patients with absent caloric responses due to bilateral peripheral vestibular lesions may still show a normal response to a rotational stimulus that contains high-frequency components.

The presence of a rotational, but not a caloric, response has important functional and prognostic implications. Thus, while rotatory chair testing is rarely helpful in lateralizing vestibular lesions, it sometimes provides important functional information that complements or confirms the results of caloric testing.

The caloric test is most useful when it is done in a high-quality laboratory and when it unambiguously reveals a unilateral or bilateral vestibular loss. Normal or mildly abnormal results on caloric testing do not allow the physician to assume that the patient does or does not have a vestibular lesion.

As in most areas of medicine, a careful history and physical examination, couched in a solid understanding of pathophysiology, is the way to diagnose accurately a vestibular disorder. The physician must specifically ask about oscillopsia—visual blurring or jumping—during head motion, which points to an abnormality in reflexes mediated by the semicircular canals. The physician must specifically ask about sensations of translation or tilt, which point to an abnormality in reflexes mediated by the otoliths. The physician must specifically ask about vertigo induced by Valsalva's maneuvers, which points to a perilymph fistula or to a craniocervical junction anomaly. Both are amenable to surgical treatment.

Perhaps the most common cause of vertigo is benign paroxysmal positional vertigo, which is diagnosed from a characteristic history and physical findings.[1] No laboratory tests are necessary to make this diagnosis, yet most of such patients undergo unnecessary magnetic resonance imaging and computed tomographic scans and electronystagmography.

Even such a basic part of the physical examination as the testing of hearing is often neglected in patients with dizziness. A unilateral hearing loss, with or without vestibular symptoms, always requires further evaluation for an acoustic nerve tumor. In fact, the most useful laboratory test in evaluating patients with vestibular dysfunction is probably the audiogram, just as vision acuity must always be measured in patients whose symptoms point to optic nerve dysfunction.

Finally, I would like to emphasize an old, simple bedside test for vestibular dysfunction that we have recently resurrected and found to be extremely useful—the induction of nystagmus after 20 seconds of vigorous head shaking.[2] When used with Frenzel lenses, this test is probably as sensitive and as reliable as the caloric test in identifying a unilateral peripheral vestibular lesion.

To summarize, vestibular function tests have a place in the evaluation of patients with dizziness and disequilibrium, but for most patients the correct diagnosis is reached by a thoughtful, physiologically oriented history and examination. With the vast number of people who are bothered by dizziness, imbalance, or both, perhaps our medical school curriculum committees should recommend more attention to the teaching of vestibular physiology and pathophysiology. How else will physicians not only understand new developments in the laboratory evaluation of vestibular function but also correctly interpret their patients' symptoms and elicit the appropriate diagnostic signs?

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Clinical and Laboratory Assessment of Patients With Possible Hemorrhagic Disorders

ALTHOUGH IT HAS ALWAYS BEEN OF CRITICAL IMPORTANCE to determine whether a patient has a defect in primary or secondary hemostasis, this clinical problem is even more urgent at the present time, because therapy for the arrest of hemorrhage with blood products should be avoided whenever possible. Disorders of primary hemostasis are mainly characterized by bleeding into superficial areas of the skin and mucous membranes and the cause is usually attributable to quantitative or qualitative platelet defects. Disorders of secondary hemostasis involve muscle tissues with dissection into fascial planes, large ecchymotic lesions in the skin, and hemarthroses.[1,2]

Patients always require screening evaluations before an operation or on being seen by a physician after an episode of hemorrhage of either a spontaneous nature or following trauma or a medical procedure. A detailed personal and ge-

netic history, superimposed on the findings of a complete physical examination, will frequently corroborate subsequent laboratory screening procedures. These should be carried out before any further medical treatment is pursued or before the patient is told that he or she may resume routine activities. Skin bruising that occurs spontaneously or in relation to minor trauma is significant because it suggests that a hemorrhagic abnormality exists. In platelet disorders, bleeding is immediate but temporary and blood loss is usually minimal. This is in contrast to disorders of coagulation, such as factor VIII or IX deficiency where hemorrhage is delayed, somewhat prolonged, and in the moderate to severe category. About 85% of congenital coagulation disorders are due to deficiencies in factor VIII (hemophilia A). About 10% are attributable to factor IX deficiency (hemophilia B), and the other coagulation defects make up the additional 5%.[1,3]

In general, if an asymptomatic patient is being evaluated before a major operation and the history is negative, the screening laboratory tests need not be elaborate.[3] Under these conditions, a platelet count, an activated partial thromboplastin time (PTT), and a prothrombin time are recommended. On the other hand, if a hemorrhagic diathesis is suspected from the history and physical examination, laboratory procedures that evaluate platelet integrity and the vascular and coagulation components of the hemostatic mechanism are necessary.

• Platelet enumeration and morphology, as well as information on the other hematologic cells from stained blood smears, are important. Erythrocyte abnormalities, such as schistocytosis, are seen in microangiopathic hemolytic anemias and can be associated with disseminated intravascular coagulation (DIC). Large platelets (megathrombocytes) suggest increased platelet turnover in response to hemorrhage, platelet destruction, or immune thrombocytopenia. The most common cause of hemorrhage in the general population is thrombocytopenia. Therefore, this diagnosis should be entertained and ruled out initially. All medications ingested recently should be evaluated as possible causes of thrombocytopenia.

• The bleeding time, appropriately determined, is almost infallible for the diagnosis of a defect in primary hemostasis. If a patient has a normal bleeding time, a platelet disorder is unlikely. A prolonged bleeding time in a patient with a normal platelet count signals a qualitative platelet abnormality and also mandates the diagnostic procedures for von Willebrand's disease. This can be pursued by measuring the components of the factor VIII complex—that is, factor VIII antigen, factor VIII coagulant activity, and factor VIII ristocetin cofactor activity as manifested by agglutination of the patient's platelet-rich plasma on adding the antibiotic, ristocetin. About 43% of patients who have a prolonged bleeding time and a normal platelet count will have von Willebrand's disease. About 27% fall into the category of vascular purpuras (platelets and coagulation normal), 16% have thrombasthenia, 7% have a "thrombocytopathy" with platelets that appear grossly abnormal, and 7% have thrombocytopathy with normal-appearing platelets. The latter two groups can also be classified as having "storage pool diseases." In these patients, a surreptitious ingestion of aspirin-containing drugs must always be ruled out, if possible.

• The prothrombin time is one of the most useful tests in clinical medicine and one that will help diagnose a coagulation defect. This test provides an overall assessment of the extrinsic pathway of coagulation. It is also used to monitor patients on anticoagulant therapy, since factor VII is the first protein to be depleted by oral anticoagulants. The prothrombin time is prolonged in deficiencies of factors II, V, VII, X, and fibrinogen. Circulating anticoagulants may also prolong the prothrombin time, and the test is also valuable for monitoring liver disease.

• The activated partial thromboplastin time (PTT) is the most important screening test for evaluating the intrinsic coagulation system. The "contact" components of the intrinsic system (factor XII, high-molecular-weight kininogen and prekallikrein) are activated by the particulate components of the PTT reagent. I should add that patients whose PTT is prolonged by the latter deficiencies are not symptomatic, and the laboratory abnormality is of no clinical significance. The phospholipid component of the PTT reagent is critical for activating factors V, VIII, IX, and XI. Even a slightly prolonged PTT must be explained before the patient is allowed to undergo any surgical procedures. The test is sensitive to factor deficiency conditions of less than 30% activity (normal range, 50% to 150%).[2]

• The thrombin time evaluates plasma coagulation on adding thrombin. Abnormalities of the fibrinogen molecule—both quantitative and qualitative—and also the presence of inhibitors will influence the thrombin time. Circulating anticoagulants, fibrinogen or fibrin degradation products, or paraproteins also lengthen the thrombin time. When the thrombin time is abnormal, confirmatory tests for identifying fibrinogen or fibrin split products should be carried out. If available, tests for fibrin monomer-fibrinogen complexes in plasma are also valuable, especially if a clinical suspicion of DIC requires confirmation.

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Case Reports

Isolated Hypogonadotropic Hypogonadism in Male Identical Twins

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IDIOPATHIC HYPOGONADOTROPIC HYPOGONADISM (IHH) is characterized by the failure of normal secondary sex characteristics to develop at the time of expected puberty. Anosmia is a common finding in patients with IHH (Kallmann's syndrome) and in their eugonadal relatives. Several reports have shown varied laboratory and clinical findings in patients with IHH suggesting a heterogeneous disorder.[1,2] It is thought to be a genetic disorder, and both X-linked and autosomal inheritance have been postulated.[3-5] Sporadic cases have also been reported.[6] In patients with IHH, abnormalities of gonadotropin-releasing hormone (GnRH) secretion are discernible. These include a complete absence of gonadotropin secretion or abnormalities in the amplitude and frequency of pulsatile gonadotropin release and altered bioactivity of the secreted gonadotropin.[7]

There is a paucity of data regarding the sexual behavior of patients with IHH before treatment. The usual recommended treatment, especially for inducing fertility, is the intravenous administration of human chorionic gonadotropin and human menopausal gonadotropin[8] or the pulsatile administration of GnRH.[9]

Herein we present the first report of sporadic idiopathic hypogonadotropic hypogonadism in identical twin brothers. Surprisingly, spermatogenesis occurred after long-term testosterone treatment in one of these patients.

Reports of Cases

Case 1

The patient, a 25-year-old male student, was first seen at age 23 because of a lack of facial hair. He had only a few hairs on the sides of his face and shaved infrequently. He had not noted any other abnormality. He did not smoke. The patient first noted hair growth in his axillary and pubic areas at 13 years of age and had libido and erections beginning at age 14 or 15. He had been married for two years when first seen, and the patient and his wife were interviewed separately concerning their sexual activity. The frequency of sexual relations was three to four times per month. Penetration was normal, and he maintained erections for 6 to 12 minutes during intercourse. He had orgasms that were normal, except that he never ejaculated.

Family history. The patient was the result of a normal pregnancy and delivery. No medication was used by his mother during the pregnancy. He had an identical twin (case 2) and a healthy sister. There is no history of abnormal sex characteristics or infertility in the parents, sister, aunt, uncles, grandparents, or brothers of the grandparents. The parents were not consanguineous. Little is known about the other family members because they live on another continent, and information about their health is scanty. No family member (except the brother) has any known medical problem. There is no known neurologic disorder, anosmia, cleft palate, or color blindness, although the relatives were not tested individually.

Physical examination. Pertinent findings on examination included eunuchoidal habitus, a height of 188 cm (74 in), scant facial hair, and abundant axillary and pubic hair but with a female escutcheon. The testes measured 2.5 by 1.5 cm and were soft. The prostate was not palpable. There was no gynecomastia. The patient had red-green color blindness. The rest of the examination, including sense of smell and a complete neurologic examination, showed no abnormalities.

Case 2

The twin brother of patient 1 had the same history and physical examination findings. His appearance was identical to that of patient 1, so that they could not be easily distinguished from each other. He was not married and had sexual relations infrequently, but with characteristics similar to those of his brother. He was also color-blind.

After the completion of the work-up, therapy for both patients consisting of the intravenous administration of testosterone cypionate (Depo-Testosterone), 200 mg every two to three weeks, was started. Patient 1 has been followed closely. His voice has deepened, and he has noted an increased amount of facial and body hair. He began to have ejaculations after about four or five months, and he also noted a somewhat increased libido, but no other change in his sexual performance.

Materials and Methods

Test Procedures

The patients were studied on the Special Diagnostic and Treatment Unit of Wadsworth Veterans Administration Medical Center, Los Angeles. On the first day of the study, a needle was inserted in the antecubital vein and was kept patent by a slow saline infusion. After a blood specimen was taken at −15 minutes and 0 minutes, both patients were given a bolus of 200 μg of GnRH and 500 μg of thyrotropin-releasing hormone (TRH). Blood specimens were then taken at 15, 30, 60, 90, and 120 minutes for luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (thyrotropin; TSH), and prolactin measurements. The preinjection serum specimens were tested for thyroxine levels, triiodothyronine (T_3) uptake, T_3 radioimmunoassay, and TSH, prolactin, LH, FSH, growth hormone, and cortisol levels. Aliquots from the −15-, 0-, and 15-minute specimens were pooled for serum testosterone measurements. The patients continued to receive GnRH, 200-μg boluses, intravenously every 8 hours for the next 72 hours.

(Geola F, Hershman JM: Isolated hypogonadotropic hypogonadism in male identical twins. West J Med 1989 Jan; 150:84-87)

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
IHH = idiopathic hypogonadotropic hypogonadism
LH = luteinizing hormone
T_3 = triiodothyronine
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone (thyrotropin)

On the second day of the study, after a baseline blood specimen was taken, the patients received 25 units of cosyntropin intravenously and 500 mg of levodopa orally. Blood specimens were drawn at 30, 60, 90, and 120 minutes for serum cortisol and growth hormone measurements.

On the fourth day of the study, the last bolus of 200 μg of GnRH was given. Blood specimens were taken at baseline, 30, 60, 90, and 120 minutes for LH and FSH measurements.

Because the patients did not ejaculate before therapy, no semen analysis was done before the testosterone injections were started. A semen analysis was done on patient 1 after 11 months of testosterone therapy. Standard radioimmunoassay methods were used for measuring hormone levels.

Patient 1 was chromatin-negative and XY karyotype. Patient 2 was not tested in this regard.

Results

The basal serum levels of the hormones are shown in Table 1. The responses to the releasing hormones are shown in Figures 1 to 5. The TSH response to TRH (Figure 1) and the cortisol response to adrenocorticotropic hormone (Figure 2) were normal in both patients. The prolactin response to TRH (Figure 3) was slightly blunted (normal peak response > 15 ng per ml). The growth hormone response to levodopa administration was normal (data not shown).

The FSH and LH responses to the initial dose of GnRH and the tenth doses (injections every 8 hours for 72 hours) are shown in Figures 4 and 5. The peak elevation of FSH levels (3.3 mIU per ml in both patients) after the first GnRH injection rose to 6.7 and to 4.6 mIU per ml in patients 1 and 2, respectively, after the tenth dose. The peak elevation of LH levels (18.1 and 15.1 mIU per ml) after the first GnRH dose, however, declined to 14.1 and 13.0 mIU per ml, respectively, after the tenth injection.

A semen analysis in patient 1 after 11 months of receiving 200 mg of Depo-Testosterone intravenously every two weeks showed a volume of 1.2 ml. The sperm count was 15,250,000 per ml. Only 20% to 30% were highly mobile. More than 50% of the sperm looked normal and mature. Serum LH and FSH levels both remained under 2 mIU per ml. The serum testosterone level rose to 450 to 650 ng per dl.

Discussion

This is the first report of identical twin brothers having idiopathic hypogonadotropic hypogonadism. The fact that none of the known relatives of the patients had disorders compatible with IHH or Kallmann's syndrome suggests that these twin brothers probably have sporadic IHH. There is no general agreement as to the mode of its transmission; it is

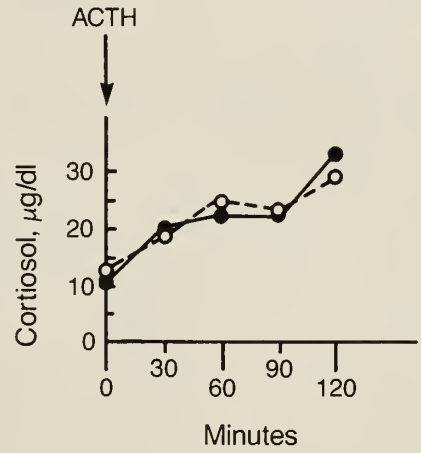

Figure 2.—The serum cortisol response to the intravenous administration of 25 units of adrenocorticotropic hormone (ACTH) is shown. •--• = patient 1, o--o = patient 2

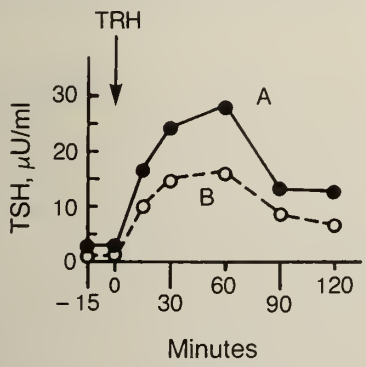

Figure 1.—The serum thyroid-stimulating hormone (TSH) levels rose after 500 μg of thyrotropin-releasing hormone (TRH) was given intravenously. •--• = patient 1, o--o = patient 2

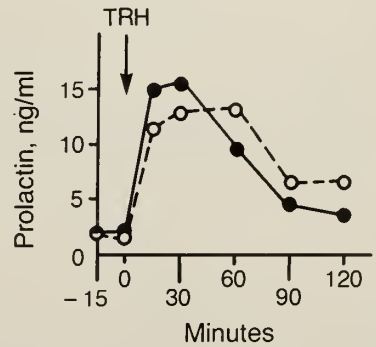

Figure 3.—The serum prolactin response to the intravenous administration of 500 μg of thyrotropin-releasing hormone (TRH) is shown. •--• = patient 1, o--o = patient 2

TABLE 1.—*Basal Serum Hormonal Levels in Identical Twins With Idiopathic Hypogonadotropic Hypogonadism*

	Testosterone, ng/dl	*LH, mIU/ml*	*FSH, mIU/ml*	*Thyroxine, μg/dl*	*Free Thyroxine Index*	*T_3 RIA, ng/dl*	*Growth Hormone, ng/ml*	*Prolactin, ng/ml*	*Cortisol, μg/dl*
Patient 1	54	1.0	1.3	8.7	9.7	134	2.4	2.3	11.1
Patient 2	44	<1.0	1.4	7.2	6.9	123	2.2	2.1	12.1
Normal values . .	350-1,050	1-15	1-15	4.5-11	4.5-11	80-180	<5	2-12	7-18

FSH = follicle-stimulating hormone, LH = luteinizing hormone, T_3 RIA = triiodothyronine radioimmunoassay

probably a genetically heterogeneous condition. Evidence for X-linked-dominant, autosomal-dominant, and autosomal-recessive inheritance has been presented.[3-8] If these monozygotic twins indeed represent sporadic cases, it can be postulated that the mutation occurred early in the cell division of the zygote—that is, at interphase. Because their paternal and maternal cousins could not be tested, the sporadic nature of the condition is uncertain.

The hormonal evaluation of our patients showed low baseline levels of LH and FSH. The initial LH and FSH increments after GnRH was administered were at or below the lower limits for prepubertal children. Subsequent testing showed mild augmentation in the FSH level and a decline or no change in LH responses to GnRH. All possible combinations of serum LH and FSH responses to various doses and modes of administration of GnRH have been reported in the literature. The various responses suggest heterogeneity in the patients who have IHH.[10-12] There may be a relationship between the gonadotropin response to GnRH and testicular size.[13]

Our patients had low basal levels of prolactin and showed slightly impaired responses of prolactin to TRH, as has been reported by Spitz and co-workers in hypogonadism.[14,15] Others, however, have shown normal or elevated prolactin levels with normal prolactin responses to TRH.[16,17] This also suggests heterogeneity in patients with a GnRH-deficiency syndrome.

It is generally assumed that a certain level of androgen is required for the initiation of adult male sexuality. Which aspects of sexuality are androgen-dependent,[18] and to what extent, is not clear. Many studies in the past several years have shown that some erectile responses are not diminished in hypogonadal men in comparison with normal men. Libido factors—that is, sexual motivation—and ejaculation seem to be androgen-dependent.[19-21] The androgen levels in these patients were in general either higher than in our patients or unreported. It also appears that the patients described in the other studies had been previously treated with androgens because it is stated that basic erectile mechanisms, once established, are no longer androgen-dependent.[22] Data on sexual function of untreated hypogonadal patients are lacking. Our patients clearly show that erections and intercourse are possible in those with low prepubertal androgen levels who have never achieved "normal" androgen levels. Ejaculations require a certain level of androgens. Our patients' libido improved with androgen treatment.

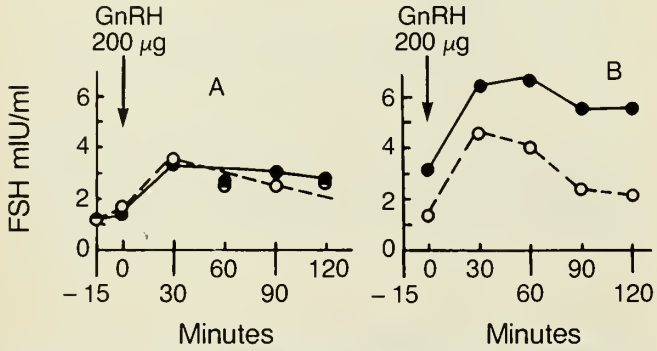

Figure 4.—The serum follicle-stimulating hormone (FSH) levels are shown after the intravenous administration of 200 μg of gonadotropin-releasing hormone (GnRH): **A**, initially, and **B**, after 72 hours of administering GnRH every 8 hours. •--• = patient 1, o--o = patient 2

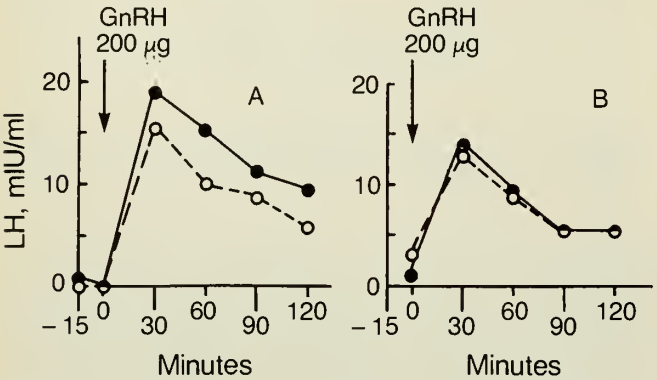

Figure 5.—The serum luteinizing hormone (LH) levels are shown after the intravenous administration of 200 μg of gonadotropin-releasing hormone (GnRH): **A**, initially, and **B**, after 72 hours of administering GnRH every 8 hours. •--• = patient 1, o--o = patient 2

According to the current concepts, normal spermatogenesis does not occur in hypogonadotropic hypogonadism unless patients are treated with gonadotropins.[23] Spermatogenesis in patients with IHH has also been achieved with the pulsatile administration of low doses of GnRH.[20] Therefore, it is surprising that in patient 1 spermatogenesis was induced by testosterone injections alone. (Patient 2 did not have a semen analysis.) Baranetsky and Carlson have reported spermatogenesis with testosterone injections in two patients with hypogonadotropic hypogonadism.[24] Both of these patients had the development of hypopituitarism at a later age and after a normal development of spermatogenesis for several years before the onset of hypogonadism. The reason for the unexpected spermatogenesis in patient 1 is unclear. The low FSH level and especially the small testicular size before treatment make the possibility of isolated LH deficiency (fertile eunuch) unlikely, although IHH and isolated FSH deficiency may be part of the spectrum of the same syndrome. Because of this unexpected finding, we recommend semen analysis of all IHH patients treated with testosterone to identify the need for contraception and particularly to determine the need for further extensive treatment, such as pulsatile GnRH or the administration of human chorionic gonadotropin and human menstrual gonadotropin when fertility is desired.

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Pasteurella multocida Infection From a Cougar Bite

A Review of Cougar Attacks

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COUGAR ATTACKS on humans are rare, with only one such case being found in the medical literature.[1]

I recently treated two people who were attacked by a pet cougar, and infection with *Pasteurella multocida* developed in one of them. This report documents that cougar bites may be a source of this infection, similar to that from other felines. In addition, a brief review of cougar attacks is presented.

Reports of Cases

Case 1

The patient, a 28-year-old woman who had recently begun working as a caretaker of a pet cougar, entered the animal's cage, accompanied by a male companion, to pet it. Almost immediately she was attacked, being bitten on the left arm and on her neck. The animal had grown up in captivity and had been declawed. The patient was not menstruating.

On presentation to the emergency department minutes after the attack, the patient was quiet and tearful, appearing frightened and smelling of ethanol. Her vital signs were normal. Her bite wounds included scattered deep abrasions and small avulsions on her left forearm and hand; a 2-cm horizontal laceration on the right side of her neck overlying the mid-sternocleidomastoid (SCM) muscle, with mild swelling over the mandible and temporomandibular joint; and superficial (nonpenetrating) abrasions and contusions of the lower anterior part of her neck. There was no crepitus about the wounds, and the laceration was not actively bleeding.

On careful inspection of the neck wound, the SCM muscle was noted to have been penetrated, but it appeared to be a minimal puncture. Her speech was fluent, and she was without stridor. A suspicion of deep penetration was lessened by the nonpenetrating nature of her other wounds and the absence of overt signs of deep injury. The results of the cardiopulmonary and remaining physical examination were normal. After a telephone surgical consultation, the neck wound was closed with interrupted simple sutures. Dicloxacillin sodium was prescribed, and the patient was discharged from the emergency department with detailed follow-up instructions and admonitions about possible sequelae.

About two hours later the patient telephoned, reporting that her voice had become hoarse and that she had coughed up some blood-streaked sputum. She returned to the emergency department and on reexamination was found to have increased swelling and some crepitus about the wound. Otherwise, the physical findings were unchanged. Radiographs of the neck showed air in the prevertebral and retropharyngeal spaces, as well as subjacent to the neck wound. A chest radiograph showed no acute abnormalities. At this time, on further questioning, she reported that the animal had shaken her in its jaws when it bit her in the neck.

An otolaryngologic consultation was obtained, and she had an esophagoscopy, laryngoscopy, and tracheoscopy, as well as a barium esophagogram, several hours later. These did not detect any perforation of the trachea or esophagus, although slight ecchymosis of the right vocal cord and some bloody mucus in the immediate subglottic area were found.

Shortly after the above procedures were completed, increased swelling, redness, and edema were noted about the neck wound. It was opened, and a substantial amount of sanguinopurulent fluid was drained. The wound was surgically extended and the neck explored. A small perforation on the posterior side of the SCM muscle was found, as well as a tract that headed in the direction of the thyrohyoid membrane. A specimen for culture was taken, and drains were placed.

Subsequently, the patient was found to have a low-grade fever and mild leukocytosis (12.7×10^9 per liter [12,700 per μl]). A regimen of intravenous cefazolin, 1 gram every six hours, was started. The fever and other signs of infection resolved within 24 hours. The wound culture was positive for *P multocida,* which was sensitive to all tested antibiotics.

Her further hospital course was uncomplicated, and she was discharged to home five days after the attack, being continued on a regimen of cephalexin, 500 mg every six hours. Her cutaneous wounds healed completely, but she was left with paresis of the right vocal cord, which is, reportedly, slowly resolving.

Case 2

The patient, a 34-year-old man who accompanied the first patient into the cougar's cage, was attacked as he grabbed the animal from behind, trying to separate it from the woman. He sustained numerous deep abrasions from bites to both upper extremities and the left knee. When seen in the emergency department, his vital signs were normal, and the re-

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sults of an examination were unremarkable except for the wounds on his extremities. These were cleaned and bandaged. A small laceration on his right index finger was closed with Steri-Strips. All his wounds healed uneventfully.

Discussion

The cougar, *Felis concolor*, is indigenous to the western hemisphere and once thrived throughout the Americas, being the most widely distributed large mammal on the American continents.[2-6] Not surprisingly, the cougar was well known to native Americans and early European settlers of the Americas. It was regarded with awe and attributed great powers, acquiring a prominent place in American folklore. Cougars were often accused of crimes they did not commit and credited with feats they could never have accomplished. Indicative of its place in American folklore, the cougar has been given more English names than any other animal, with a partial list of these including mountain lion, puma, panther, painter, catamount (short for cat-of-the-mountains), silver lion, purple panther, red tiger, brown lion, deer tiger, Mexican lion, American lion, mountain screamer, and Indian devil.[2,6] Because of its retreat to sparsely populated areas and its brush with threatened extinction in the eastern United States, the cougar for many people has come to symbolize the "wild West" and wilderness.

Despite its frequent mention in the popular literature, there is essentially nothing in the medical literature about cougar attacks. The one case report found after an extensive review involved a 3-year-old California girl who was attacked by a pet cougar and suffered massive head and facial trauma.[1] This report contained no details of the attack, however, focusing instead on the surgical repair of the wounds.

From a clinical perspective, case 1 underscores two main points.

First, *P multocida* should be considered as a contaminant and potential pathogen in bite wounds from cougars. This has not been previously reported, although *P multocida* infection is a well-known complication of domestic cat bites, being the pathogen in 30% to 50% of cases of infected feline bites.[8-20] *P multocida* infection also has been reported as a complication of lion,[18,19,21,22] tiger,[22] lynx,[23] and leopard (African "panther")[24] bites.

Similar to the pneumococcus in humans, *P multocida* is a common commensal and pathogen of the respiratory tract of many animal species.[8,9,19,20] It has been cultured from the upper respiratory tracts of 52% to 70% of healthy domestic cats,[23,25] and its identification rate in sick animals may be as high as 100%.[20]

P multocida is a pleomorphic, gram-negative, nonmotile, bipolar-staining coccobacillus that was biochemically and morphologically characterized by Pasteur in 1880 after it had been identified as the cause of fowl cholera a few years earlier.[9] In 1913 it was first reported to cause human illness in a farmer's wife suffering puerperal fever and septicemia. Infection from a cat bite was first reported in 1930. Since then, its importance as a cause of animal bite wound infection has been recognized, with feline bites accounting for 60% to 80% of *P multocida* infections.

P multocida infection most often presents as a rapidly developing cellulitis at the site of an animal bite or scratch wound.[8,9,11,13,20,25] *P multocida*-infected wounds have the typical manifestations of a cellulitis, with regional adenitis, purulent discharge, and low-grade fever being common. There is nothing that overtly characterizes these wound infections except their rapid development. Indeed, bite wounds that become infected in less than 24 hours are likely to be due to *Pasteurella*.

P multocida is a problematic pathogen, though, because of its opportunistic nature and potential to cause chronic local infection of deep tissues, septicemia, and a wide variety of other infections, including osteomyelitis, septic arthritis, meningitis, brain abscess, subdural empyema, endocarditis, pyelonephritis, appendicular abscess, peritonitis, pneumonia, and lung abscess.* The occurrence of unusual infections such as epiglottitis,[12] mycotic aneurysm,[14] septic prosthetic joints,[15] and infection of vascular grafts[29] has also been reported. Patients with chronic bronchopulmonary or liver disease, especially if elderly, are predisposed to disseminated infection.[16,17,27,30-33]

P multocida is unusual for a gram-negative bacterium because of its sensitivity to penicillin, with this drug or one of its derivatives being the treatment drug of choice.[9,10] In cases of penicillin allergy, tetracycline, chloramphenicol, the cephalosporins and, possibly, the combination of trimethoprim and sulfamethoxazole are the preferred alternative drugs. Erythromycin is generally effective, although some treatment failures have been reported with this agent.[11] Because plasmid-mediated antibiotic resistance has occurred with this pathogen, sensitivity testing is necessary in all cases.

The second point that should be made regarding case 1 is that, despite having a relatively benign appearance, cougar or other large cat-bite wounds of the neck—which is probably the cats' most common point of attack—should be assumed to penetrate deeply until proved otherwise, especially in view of their propensity to shake their victims. It is probably worthwhile to routinely take radiographs of the neck as part of the initial evaluation of all such cases.

Unfortunately, because of the paucity of clinical experience with such wounds, it is impossible to make any empirical recommendations about primary wound closure of cougar bites. Primary closure after an appropriate debridement would seem to be reasonable, though, because these injuries are much more like dog bites than domestic cat bites, and primary closure is generally accepted for non-high-risk dog bites.[10] As with domestic cat bites, it probably is prudent to routinely prescribe antibiotics in these cases because of the high risk of wound infection. The preferred prophylactic antibiotic is penicillin.[9]

From a broader public health perspective, these and other recent cougar maulings raise a number of public safety issues. Unfortunately, limited data about the size and range of the cougar population and the circumstances under which they attack complicate addressing these issues.

Solitary, shy, and secretive by nature, cougars are extremely difficult to study, so knowledge about their population size and behavior is less than for many other wild animals. Indeed, the "conventional wisdom" about cougars is based on relatively little observation and substantial inference. It is clear, though, that their range and numbers have diminished substantially in the past two centuries commensurate with predator control activities, sport hunting, and pronounced habitat changes.

Currently, variable-sized populations of cougars are

*References 9, 11-13, 16, 17, 22, 25-28.

found in the 11 western states, South Dakota, Texas, and western Canada.* A vestigial population lives in the swamps of Florida, and small breeding populations probably exist in Minnesota and central Canada. Occasional unverified sightings have also been made in Maine, Vermont, New Hampshire, Massachusetts, New York, New Jersey, and Michigan. Interestingly, in recent years there has been an increasing number of sightings of cougars in or near urban areas in California, Colorado, and other western states.

Next to the jaguar, the cougar is the largest feline in the Americas, with adults typically weighing 45 to 68 kg (100 to 150 lb) and measuring 1.8 to 2.4 m (6 to 8 ft) from the nose to the tip of the tail.[2,5] The largest cougar on record was a male shot in Arizona that weighed 125 kg (276 lb).[2,6] The cougar is well designed for concealment and stealth and is the most efficient land predator of the Americas next to the grizzly bear.

Despite its wide distribution, large size, and predatory behavior, and notwithstanding its prominent place in American mythology, the cougar has never constituted a serious threat to humans. Indeed, documented attacks on humans by wild cougars are notably infrequent. Only 66 were reported between 1750 and 1985,[7] of which 23 (35%) were fatal. Most of these attacks (39 of them, or 59%) were reported from the United States, with Canada reporting the next most—primarily from Vancouver Island. In the US, 31 (80%) of the attacks occurred in the 11 western states. Important to note, though, these incidents almost certainly were underreported in the past, especially before 1900.

Two more wild cougar attacks occurred in the US in 1986; both of these were in the Ronald W. Caspers Wilderness Regional Park in Orange County, California—just south of Los Angeles. The first was of a 5-year-old girl in March, and the second was of a 6-year-old boy in October. An additional close encounter involving a child in the same park was reported in October 1986. Before these, no wild cougar attacks on humans had been reported in California since 1925.[7] These two cases brought to eight the number of attacks on humans reported from California, representing 12% of all attacks by wild cougars reported since 1750; two of these involved multiple victims.[7] Additional attacks by pet cougars are known to have occurred, but these data have not been systematically collected.

Including the two cases described here and the previously cited case,[1] at least 14 people are known to have been attacked by cougars in California since 1750, 9 of whom have been children (64%). Ten of these attacks (71%) were fatal, with two of the fatalities—both from one attack—being due to rabies.[34] (This is the only recorded instance of humans contracting rabies from a cougar bite.)

Notwithstanding the limitations of current data, several points can be made about cougar attacks. The recent maulings in California exemplify some of these points.

First, cougar attacks on humans are rare, but they can and do occur when the right circumstances are present. Unfortunately, the circumstances that may predispose humans to being attacked are not fully understood. Sickness or starvation may predispose some animals to attack, but healthy animals are known to have been involved in more than 40% of the reported attacks.[7] Further, observations in this regard are often misleading because young, healthy cougars may appear emaciated or "starved." Unlike what has been postulated regarding bear attacks, available data do not indicate that menstruating women are at greater risk of cougar attack, although there are few data in this regard.

A substantial number of cougar attacks have involved pet animals, although detailed statistics in this regard are not available. These attacks seemingly have most often involved persons unknown to the animal or children, who typically have either startled or, albeit unknowingly, threatened the animal. The wisdom of keeping cougars as pets, especially in households containing children, should be seriously questioned.

Second, there seems to have been a significant increase in the size of the cougar population in California in the past 15 years—that is, since California imposed a moratorium on killing cougars in 1971. (California is the only state to have enacted such a moratorium.[7,35]) Considerable controversy surrounds estimates of the absolute size of the state's cougar population, however, and this controversy is a central point in the current debate about the resumption of cougar hunting in California. In the northeastern US, there may also be an increase in the cougar population, while in other states, cougar populations appear to be stable or declining.

Third, overlap between human and cougar habitats has substantially increased. This has occurred for several reasons. The cougar, which is known to be highly adaptable, appears to be expanding its range, similar to what has occurred with coyotes in California and some other western states in recent years. Whether this is due to their rising numbers, such as may be the case in California, and, thus, dispersal resulting from competition for limited habitat, or for some other reason is not clear. Similarly, there has been a notable proliferation of human activity in rural and wilderness areas in the past two decades. This includes recreational activities such as hiking and camping, as well as housing development and harvesting of timber and other natural resources. Such activities allow cougars to gradually become more accustomed to people as an element of the environment and, thus, may reduce their fear of humans. They also place people in settings where they may be unknowingly at an increased risk of attack. Whatever the case, the growing overlap of human and cougar habitats increases the likelihood of future attacks and indicates a need for a greater appreciation of these animals by wilderness enthusiasts, the posting of warning signs in areas known to harbor the animals, and the implementing of other preventive measures appropriate to the area and activity involved.

Finally, data from recent years indicate that young children are at a higher risk for cougar attacks than adults. This is probably a result of their small size and characteristic excited conversation, quick movements, and vigorous physical activity, all of which may stimulate attack behavior in the cougar.[7] In view of the increased sightings of these animals in or near urban areas and, in some areas (California), reports of increased livestock kills attributed to cougars, it seems clear that adult supervision and extra caution should be exercised over children playing in areas thought to harbor these animals. Having adults accompany children in "cougar country" is especially important in light of the observation that cougars have rarely attacked groups of people containing adults, although the same cannot be said for groups of children without accompanying adults.[2,7]

*E. Lee Fitzhugh, Wildlife Specialist, University of California, Davis, Wildlife Extension, reviewed the manuscript and provided helpful information on the distribution and behavior of cougars.

Overall, the risk of attack from cougars in the US is extremely small, with the greatest risk seeming to be among people who keep these animals as pets and, recently, among people—especially children—visiting intensively used wilderness areas and rural areas where there have been increases in the population of these animals. Even in these settings, though, the danger is very slight.

Far from being an innately vicious animal, the cougar is a shy and retiring creature that happens also to be an especially effective predator and one that is exceptionally well adapted to its environment. Indeed, the cougar is a magnificent animal worthy of great respect and society's protection. It is hoped that by better understanding these animals and the circumstances under which attacks have occurred in the past, humans can learn to share habitats with cougars without either species suffering untoward consequences.

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Correspondence

Behçet's Disease ('Silk Route Disease') and Mitral Valve Prolapse

To THE EDITOR: I enjoyed reading Dr D. Geraint James' review article on Behçet's disease, which he elected to rename "Silk Route disease," in the April 1988 issue.[1] In his discussion of the cardiovascular involvement, which is predominantly vascular, he failed to mention mitral and aortic valve prolapse. Because he named Behçet's disease "Silk Route disease" and because the association of valve prolapse and Behçet's disease was first reported in China,[2] I think it is appropriate to point out such an association.

According to Shen and colleagues, valve prolapse occurred in 50% of their patients with Behçet's disease. These authors postulated that the valve prolapse, either mitral or aortic, may have been the result of structural damage and functional derangement caused by the underlying vasculitis of Behçet's.[2]

Whereas the association of valve prolapse and Behçet's disease may be either causally related or coincidental,[3] it is important to keep it in mind in view of the fact that although this disease is relatively rare in the United States, mitral valve prolapse is common.[4,5] Although mitral valve prolapse is rather benign, aortic valve prolapse may not be; the aortic valvular regurgitation from aortic valve prolapse may have important prognostic consequences. It seems logical, therefore, in a multisystem disorder like Behçet's disease, to look for the presence or absence of mitral or aortic valve prolapse, or both, by either careful auscultation or routine echocardiography.

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Health Maintenance Organizations

To THE EDITOR: Dr Philip Alper's article on health maintenance organizations (HMOs), "Trust at Risk," in the October 1988 issue[1] contains some notable inaccuracies, at least as far as Kaiser-Permanente, the largest HMO, is concerned.

I am retired after 30 years as a Kaiser-Permanente partner. As a retired physician, I will not be affected financially by the outcome of this debate. The record, however, should be corrected.

Dr Alper stresses the theory that there is a barrier to necessary consultations with specialists in HMOs. There has never been any barrier to referral of patients to specialists in Kaiser-Permanente. In fact, a large percentage of initial appointments are made directly with specialists by the patients themselves, with no physician screening or need for approval. The number of physician referrals to specialists is not reflected in the financial "balance sheet" nor in the annual income of the physicians. The Kaiser-Permanente staff includes ratios of generalists to specialists that reflect the ratios in the community. For this reason, referrals to specialists in Kaiser-Permanente occur at least as often as in the community.

Not only is there no such barrier as claimed, but, in addition, the lack of added financial burden on the patient, when consultation with or transfer to a specialist is indicated, results in freer and more numerous consultations. Moreover, the lack of specific individual fees for specialized services, such as operations, results in an absence of motivation to operate when indications are borderline or inadequate. The prepaid system and direct unscreened access to all professional services lead to high quality medical care at low cost.

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Malignant Melanoma and Redheads

To THE EDITOR: In an otherwise excellent article in the July 1988 issue, Dr Robert Rifkin and colleagues say that

> It should be noted that it was uncommon for patients with malignant melanoma to have red hair (13%). There is a common misconception that persons with bright red hair and freckles are those in whom malignant melanoma is most likely to develop. As can be seen, this was not borne out by our data.[1]

This information was immediately picked up by the popular press and published (*Salt Lake Tribune*, July 24, 1988, p A5). Unfortunately, this statement propagates a dangerous misconception, one not justified by the author's data.

In a study of the projected images of hair color, a survey of the population of seven American cities including Denver and Salt Lake City showed that 57.2% had brown hair, 25.7% were blonde, 11.1% had black hair, and only 6.0% were redheaded.[2] As can be seen in Table 1, the authors' data actually show that redheads are more than *twice* as likely to have a malignant melanoma as would be expected if hair color were not a factor. Since their study included auburn hair and the image study did not, two analyses can be made (Tables 1 and 2). The first eliminates auburn hair from the analysis, and the second makes the conservative assumption (at least from the authors' original statement) that auburn in the image study was labeled as brown. The hypothesis that

TABLE 1.—*Hair Color Distribution by Melanoma and Expected Occurrence, Auburn Included*

	Patients,* N=208		Expected,			
Hair Color	Number	Percent	Number	Percent	χ^2	%
Brown	108 (116)†	52 (58)†	119	57	0.08	<1
Blonde	54	26	54	26	0.00	0
Red	26	13	12	6	16.33	75
Black	12	6	23	11	5.26	24
Auburn	8	4	...	...	....	...
				χ^2 =	21.67	100

*Data from Rifkin et al.[1]
†Numbers in parentheses are those given for auburn hair color.

TABLE 2.—*Hair Color Distribution by Melanoma and Expected Occurrence, Auburn Excluded*

Hair Color	Patients,* N=200 Number	Patients,* N=200 Percent	Expected, Number	Expected, Percent	χ^2	%
Brown	108	54	114	57	0.32	2
Blonde	54	27	52	26	0.08	0
Red	26	13	12	6	16.33	77
Black	12	6	22	11	4.55	21
				χ^2 =	21.28	100

*Data from Rifkin et al.[1]

malignant melanoma is randomly distributed among hair colors is strongly statistically rejected—$\chi^2 = 21.28$, degrees of freedom (df) = 3, $P < .0001$ if auburn is removed; $\chi^2 = 21.67$, $df = 3$, $P < .00009$ if auburn is distributed only to brown. Even a simplified hypothesis that the percent of malignant melanoma matched the percent of redheads independent of other hair colors would be rejected by the data—$z = 4.168$, $P < .00003$ if auburn is removed; $z = 4.251$, $P < .00002$ if auburn is distributed only to brown.

These authors' warning that physicians should recognize persons at high risk should *especially* include those with red hair.

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* * *

Dr Robinson Responds

To THE EDITOR: We thank Dr Clayson for his letter. In reviewing his data cited for various proportions of hair color in "seven American cities," we note that these studies were done exclusively on women "passing a set location in public places in seven American cities," which are unnamed. We doubt that this is a truly representative sample of hair color that can be compared with the Colorado population from which our subjects were drawn.

Regardless, we agree that persons with red hair are at higher risk for the development of malignant melanoma than those with other hair colors. We would, however, point out once again that the commonly held belief that most patients with malignant melanoma have red hair is incorrect. Most patients in whom malignant melanoma develops have brown or blonde hair.

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Physician Stress

To THE EDITOR: Recent articles in medical journals about physician stress led to these comments.

When reviewing the records of 14 physician patients seen in my office between 1960 and 1987, I found that 11 of the 14 had emotional problems primarily reflecting difficulties in their medical work. There were 12 men and 2 women; 12 whites and 2 blacks; 6 family physicians and 8 specialists; 11 employed and 3 in private practice. Ages ranged from 28 to 54 years. Diagnoses were anxiety and depressive or adjustment disorders. None were psychotic, and only one had a substance abuse problem.

McCue emphasized in 1982 that physician stress is related to daily clinical encounters with sexual problems, suffering, death, fear, pain, uncertainty, and problem patients.[1] In 1986, two thirds of physicians surveyed felt more stress during the previous five years than in former years.[2]

Unfortunately, the current emphasis is on pathogenic childhood experiences and largely ignores stressful experiences on the job. This is the perspective of Vaillant and colleagues, who reported that physicians with happy childhoods were better adjusted as adults and had less mental and physical illness.[3] This leaves stressed physicians with little alternative but to blame themselves and feel powerless to change their situation.

A major cause of physician stress in the work environment is the ineffective and wasteful way health care is organized and delivered. Destructive and costly competition and maldistribution of care cause needless conflict and frustration for physicians in the office, clinic, and hospital. Improving the health care system would go a long way in preventing physicians' stress problems.[4] Whether a national health plan can achieve this is now being vigorously debated.[5]

At the present time, many organizations have stress reduction programs. Don't physicians need these, too?

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Possible Neuroleptic-Induced Resistance to the Human Immunodeficiency Virus

To THE EDITOR: Neuroleptics of the phenothiazine, butyrophenone, and thioxanthene class are known to inhibit the intracellular action of calmodulin, a multifunctional calcium binding protein that controls cell pinocytosis and, consequently, the penetration of virus particles through lymphocytic membranes. Furthermore, it has been shown in vitro that calmodulin antagonists decrease the infectivity of Epstein-Barr and feline leukemia viruses[1] in the cytoplasm of B lymphocytes by depressing the endocytic process that regulates infectivity in these cells.

The cytotoxic and antiproliferative actions of phenothiazines towards malignant leukemic cells have been attributed to their marked anticalmodulinic properties. Calmodulin mediates a large number of enzymatic and functional processes such as protein kinase, adenosine triphosphatase, methyltransferase, microtubule assembly, and formation of normal as well as abnormal cell proliferation.[2]

We have analyzed the medical and social history of 11 patients with mental disorders (10 men and 1 woman, age range 24 to 32 years) infected with the human immunodeficiency virus (HIV) and found that in none of them had the

acquired immunodeficiency syndrome (AIDS), AIDS-related complex (ARC), or AIDS dementia complex developed several years after contracting the infection. All had received one of the following neuroleptics on a regular basis:

thioridazine (Mellaril)	50 mg twice a day
haloperidol (Haldol)	20 mg twice a day
thiothixene (Navane)	20 mg 3 times a day

All of these patients had similar social and psychiatric histories characterized by innumerable promiscuous homosexual and heterosexual contacts in an area of high endemicity (San Francisco), complicated by poor hygiene and living conditions and inadequate nutrition. Such patients are prime candidates for the development of AIDS and related conditions. All of these patients appeared to be in excellent physical condition with normal blood counts. Only two showed relative lymphopenia and an altered ratio of helper and killer T lymphocytes. None of them showed any AIDS-connected pathology. The fact that the disease is late in onset or may not manifest itself at all could possibly be attributed to inhibition of calmodulin due to regular exposure to neuroleptics or to blockade of dopamine receptors on lymphocytic membranes. It should be noted also that inactive phenothiazine metabolites, such as the sulfoxides, which are devoid of central nervous system effects, inhibit intracellular calmodulin functions.

Clearly, further epidemiologic studies are needed to establish whether or not neuroleptics possess a protectant effect on HIV infections. We hope that this preliminary report will stimulate such studies in view of the obvious therapeutic potential in nonpsychotic patients infected with this virus.

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Post-lumbar Puncture Headache

To THE EDITOR: The article by Raymond and Raymond on post-lumbar puncture headache in the May 1988 issue[1] reminded me of my own experience with palliation of this condition. Four years ago at age 44, I developed right-sided neck pain and headache with partial left ninth cranial nerve mononeuritis. The results of the initial blood studies and computed tomographic scan were negative, and after ten days of symptoms a lumbar puncture, which also proved negative, was done with a No. 20 needle. Despite an 18-hour period of post-tap recumbency, I had a new type of headache the next morning. Headache number two was relieved promptly upon assuming recumbency. There then followed a period of ten days during which I learned that I could remain upright only five minutes or less before the headache and nausea got the better of me.

An epidural blood patch was discussed several times with my neurologist, but his uncertainty as to the cause of headache number one led him to advise recumbency and analgesics. At this point I reasoned that because gravity was the enemy, I would try the other terrestrial equivalent of weightlessness besides bed rest—water immersion. In the backyard spa I was able to sit up without symptoms. Whether this was a consequence of a "weightless" state or the hydrostatic equivalent of an abdominal binder, as mentioned in the article, I am not certain.

The original symptoms were clarified when I heard a left carotid bruit after my soak. An angiogram the next morning revealed bilateral internal carotid arterial dissections that healed without residual symptoms. Treatment was aspirin and four weeks of bed rest. By the time I was up and about, the post-lumbar puncture headache had resolved.

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Low Back Pain

To THE EDITOR: I read with interest "Managing Low Back Pain—A Comparison of the Beliefs and Behaviors of Family Physicians and Chiropractors" in the October 1988 issue.[1] Back pain, as the authors describe, is a very common and costly health problem. Research designed to gather information on the diagnosis and treatment of back pain is certainly needed.

The article indicated that there is little known about the relative cost-effectiveness of chiropractic care versus allopathic or osteopathic care. Comprehensive comparisons were made between chiropractors and family physicians. Unfortunately, no statistics were presented that differentiated between allopathic and osteopathic family physicians.

Osteopathic physicians receive training in manipulative therapy as well as drug therapy for back pain. Further analysis of these data and future studies specifically identifying and analyzing osteopathic care could yield important information regarding the effective management of low back pain.

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Ethical Issues in the Treatment of Sexual Dysfunction in HIV-Seropositive Patients

To THE EDITOR: Ethical issues in the treatment and care of patients with the acquired immunodeficiency syndrome (AIDS) are far reaching. In caring for a number of patients in various stages of the disease over the past two years, I have found their plight a precarious one. The clinical presentation of these patients varies widely with clinical setting and population and from patient to patient. It seems the ethical issues in daily clinical care often cannot be generalized, specified, or codified, as can such issues in research or policy settings. Such an ethical dilemma is shown in the following case presentation.

A 55-year-old man was referred to our support group after expressing extreme anxiety associated with the revelation of his positive test results in an infectious disease clinic. The patient presented to our group stating that, in addition to being found to have the human immunodeficiency virus

(HIV), he also suffered from hypertension and diabetes mellitus.

The patient also revealed that he was being treated in a sexual dysfunction clinic for erectile dysfunction secondary to peripheral vascular disease associated with diabetes. Before his diagnosis of HIV seropositivity, the patient had been promised a vacuum-type device, called an "Erectaid," that suctions blood into the penis. Then the penis is banded to prevent blood from escaping, thereby increasing the amount and duration of erection.

That this new diagnosis had presented a dilemma to the sexual dysfunction clinic staff was obvious, as the patient complained to the group that the clinic was "stalling" in giving him the device that had been promised earlier. This patient had frequented bathhouses before his positive test results and was ambivalent regarding his sexual practices in the future. He made no commitment to the sexual dysfunction clinic staff to use his newly functional penis inside a condom.

The ethical issues involved in this case are clear. Do we as physicians have the right to withhold treatment of sexual dysfunction in patients who have a potentially lethal disease that can be transmitted during intercourse? Should this "right" be contingent upon whether or not the patient agrees to practice "safe sex"? By what measure can we be responsible if a patient does infect another person while using a device to enhance sexual function? If we do not treat sexual dysfunction in HIV-seropositive patients, are we infringing upon the rights of the individual, as this patient alleged? And what of society and our responsibility to the health of potential partners? Are a patient's verbal assurances sufficient, or does there need to be a formal psychiatric assessment of a patient's stability and reliability?

As the AIDS epidemic continues, it will present us with conflicts such as the dilemma described that reflect the ambiguities arising when treating HIV-infected patients.

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Radiologic Case

Mass Lesion in an Intravenous Drug User

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A 22-year-old woman was admitted to hospital for evaluation of fever, nonproductive cough, and right-sided chest pain for five days. She had not had any major medical problems in the past. There was a history of alcoholism and intravenous drug addiction for the past several years.

On physical examination she had fever, tachycardia, and multiple needle marks on the skin. She refused consent for testing for the human immunodeficiency virus.

A chest x-ray film was taken (Figure 1).

What are the findings? What is the diagnosis? How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION.

Figure 1.—The posteroanterior chest x-ray film shows a well-circumscribed, smoothly marginated, rounded consolidation projected over the right hilar area.

(Pandya K, Tuchschmidt J, Gordonson J, et al: Mass lesion in an intravenous drug user. West J Med 1989 Jan; 150:95-96)

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DIAGNOSIS: Round pneumonia

Figure 2.—The chest x-ray film shows extension of the infiltrative process (shown in Figure 1) to involve most of the right middle and lower lobes.

Figure 3.—A follow-up chest film taken of the same patient as in Figures 1 and 2 shows clearing of the infiltrative process.

Because of the patient's history of intravenous drug use, acquired immunodeficiency syndrome-related neoplasms and infections, as well as other causes of lymphadenopathy, were considered. A second chest x-ray film showed extension of the infiltrate to involve most of the right middle and lower lobes (Figure 2). Examination of a sputum specimen did not reveal any predominant organism. The patient, however, was treated with penicillin and showed a good clinical response, as well as clearing on a follow-up chest film (Figure 3).

Pneumonic consolidation will occasionally present as a rounded mass lesion (spherical, or round pneumonia), rather than as a typical segmental or lobar infiltrate. Round pneumonia is more common in children than in adults. In the early course of the infection, the process is predominantly one of alveolar inflammation and exudation. It spreads by direct extension through the intra-alveolar channels (pores of Kohn and channels of Lambert). This can produce a nonsegmental distribution and smooth borders. Later, with centrifugal and peribronchial spread, the pneumonia usually becomes segmental or lobar and then has the typical radiologic appearance seen in the adult population. If the initial x-ray film is taken early enough in the course of the disease, round pneumonia can cause clinical confusion.

In summary, round pneumonia produces a well-circumscribed, smoothly marginated "mass" early in the course of clinical symptoms. It occurs more commonly in children than in adults. Considering this disorder in the differential diagnosis of masses on a chest film, in the proper clinical setting, may prevent unnecessary workup and obviate the use of invasive procedures.

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Topics in
Primary Care Medicine

Management of Marine Stings and Scrapes

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

As more people swim, snorkel, and scuba dive, the need has increased for primary care providers to be able to recognize and treat marine bites and stings. In this article we review the more common marine animals that can pose a threat to humans: the Portuguese man-of-war, jellyfish, sea anemones, sponges, sea urchins, stingrays, corals, catfish, and lionfish (Figure 1). Our focus will be on symptoms and the initial management of these envenomations.

Portuguese Man-of-War, Jellyfish, and Sea Anemones

Having in common a similar stinging cell, the Portuguese man-of-war, the true jellyfish, the box jellyfish, and the sea anemone are among the major sources of marine envenomation today. The Portuguese man-of-war inhabits the warmer waters of the Atlantic and can often be found off the Florida coast or in the Gulf of Mexico. Its smaller Pacific counterpart, the bluebottle, accounts for many marine stings in Hawaiian waters. Numerous species of true jellyfish can be found throughout all waters along the United States' coastline. The box jellyfish may well be the most poisonous animal in all marine life and is found primarily off the coast of Queensland, Australia, or in the open seas of the Indo-Pacific. The sea anemone is commonly found in tidal pools and induces its sting when the unsuspecting victim brushes against it. Like the man-of-war and the jellyfish family, the sea anemone contains stinging nematocysts.

The nematocyst is a cell containing venomous fluid within which is a threadlike projection. Once the nematocyst is stimulated, this needlelike tube lashes out, releasing its venom into a victim and inflicting a sting that can lead to both local and systemic reactions. The venom contains many polypeptides, quaternary ammonium compounds, histamine, 5-hydroxytryptamine, and catecholamines.

Some jellyfish tentacles reach 40 meters in length, are often transparent, and pose a significant hazard to unwary swimmers. Man-of-war tentacles can each contain as many as 750,000 stinging nematocysts. A dead man-of-war on the beach or any broken tentacles can retain live nematocysts able to sting for several days.

The severity of the sting of a Portuguese man-of-war, jellyfish, or anemone depends on several factors: the animal involved, the amount of venom and the nature of its toxicity, the size of the sting over the surface area of the victim, and the victim's general health. Mild stings generally produce a localized reaction, with the victim initially experiencing burning sensations and paresthesia at the site of envenomation. Pain may radiate throughout a given limb into the groin or axilla. Pruritus and localized erythema often develop at the site of tentacular imprinting. Wheals and a papular dermatitis can erupt within the first several hours and remain for as long as a week. Sea anemone and selected jellyfish stings can often progress to skin necrosis with ulcerations.

A Portuguese man-of-war encounter may lead to a discharge of hundreds of thousands of nematocysts in a single sting, occasionally leading to significant systemic reactions but rarely resulting in fatalities. Severe man-of-war, jellyfish, and anemone stings can produce neurologic sequelae ranging from malaise and headache to seizures, delirium, coma, and paralysis. From a cardiopulmonary standpoint, cardiac arrhythmias, bronchospasm, laryngeal edema, and respiratory failure can develop. Gastrointestinal complaints include nausea and vomiting. Victims may complain of severe musculoskeletal spasm and cramping.

Box jellyfish stings, which contain a cardiotoxin, are often lethal: 15% to 20% of box jellyfish stings prove to be fatal; death can occur in less than 30 seconds.

Treatment modalities are described in Table 1. For treating a person stung by a jellyfish or a Portuguese man-of-war, the affected site should be immediately bathed in seawater if a detoxicant is not readily available. Applying fresh water can induce further toxin discharge and stinging, with worsening of symptoms. Definitive care of the sting is directed at methods that inactivate the toxin and remove the tentacles.

Applying vinegar (5% acetic acid) is now the treatment of

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choice to inactivate nematocyst discharge of most species of jellyfish, the Portuguese man-of-war, and sea anemone. Baking soda is the suggested first line of therapy for Chesapeake Bay sea nettle stings. The wound site is then washed clean, and the detoxicant may be reapplied if necessary. In a pinch, a paste of baking soda may be applied and removed by scraping the area with a knife or shell edge. Tentacle fragments adhering to the skin should be removed with any available instrument but are best dislodged by using a razor for shaving. Direct physical contact by the rescuer should be avoided. The site of the sting should not be rubbed.

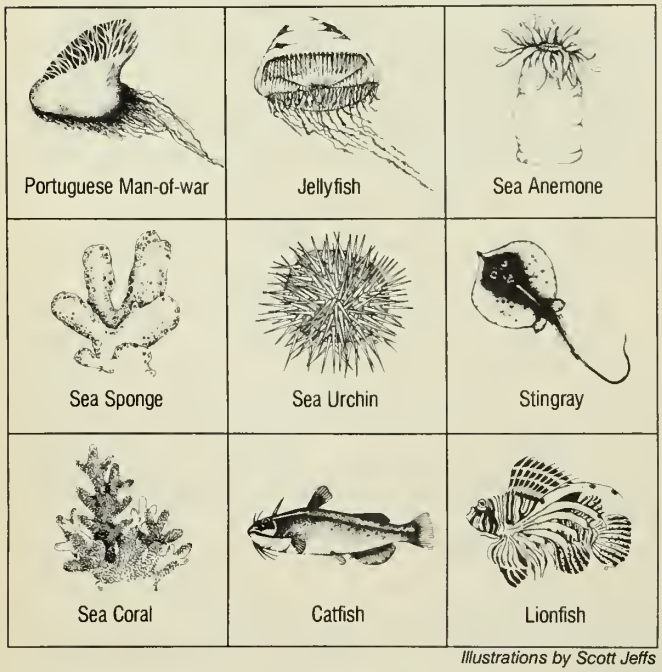
Alcohol has been a treatment modality used in the past; recent studies indicate, however, that its use can lead to substantial nematocyst discharge in vitro. Many other agents, including dilute ammonia and aluminum sulfate, have also been used with variable success. The use of papain, found in meat tenderizers and which purportedly cleaves the toxin proteins, is viewed with skepticism by some authorities.

After the nematocysts have been inactivated and removed, additional supportive measures can be addressed. General use of prophylactic antibiotics is not recommended. Oral analgesics are given for pain relief; occasionally, parenteral agents are necessary. Administering antihistamines and epinephrine can effectively treat allergic phenomena. Other topical medications, such as local steroid creams or anesthetics, may resolve local discomfort. Daily soaks with Burow's solution may be helpful. Some experts advocate tetanus prophylaxis. Occasionally severe systemic reactions develop, and supportive care is directed at specific symptoms as transportation to the nearest hospital or care center is arranged. There are no specific antivenoms available for treating North American jellyfish, Portuguese man-of-war, or sea anemone stings; however, there is a specific antidote for the deadly box jellyfish sting.

In the event of a box jellyfish envenomation, antivenom, obtained through hyperimmunizing sheep, may be given parenterally, preferably intravenously. Ampules containing 20,000 units of antivenom and available through Commonwealth Serum Laboratories, Melbourne, Australia, may be administered intravenously over five minutes. The antivenom diminishes the localized reactions produced by the box jellyfish, as well as the more severe systemic effects. Some experts also recommend applying a proximal venous occluding tourniquet in addition to giving the antivenom.

TABLE 1.—*Treatment of North American Jellyfish and Portuguese Man-of-War Stings*

Bathe site in seawater
Apply 5% acetic acid (vinegar)
For the Chesapeake Bay sea nettle, apply a baking soda slurry
Remove tentacles with a razor blade or other instrument
Use analgesics for pain relief
Soak daily in Burow's solution for comfort
Consider giving topical corticosteroids



Illustrations by Scott Jeffs

Figure 1.—The various marine animals are depicted that can inflict wounds, bites, or stings on unwary swimmers, snorkelers, or scuba divers.

Corals

The true corals do not sting their victims but cause direct trauma through the development of "coral cuts." These warm water organisms, structured on a skeleton of calcium carbonate, are responsible for the development of coral reefs, which are often explored by divers and snorkelers. As the victim brushes against the reefs, the knifelike coral can produce sharp cuts, with pruritus, erythema, and urticaria developing at the wound site. Cellulitis with ulceration can occur, leading to necrosis. These lacerations heal slowly, with the victim often experiencing prolonged localized discomfort. This may be due to bacterial infection, contamination of the wound site with microparticles of coral or sediment, or possibly to toxin effects.

Coral cuts are primarily treated with irrigation and debridement. The site of abrasion or laceration should be cleansed with soap and water. Irrigating with a saline solution is important to remove any foreign material and to prevent secondary infection or the development of a foreign body granuloma. Hydrogen peroxide has also been used as a means of removing small coral particles from the wound site. Wounds are subsequently treated with wet to dry dressings using topical antiseptic solutions. While further well-designed clinical studies are needed, current recommendations regarding antibiotic therapy for coral cuts suggest that patients with normal immune states probably require no prophylaxis. Patients who have a compromised immune system should receive a combination product of trimethoprim and sulfamethoxazole, ciprofloxacin, or tetracycline to cover marine infections due to such organisms as *Vibrio* or *Alteromonas* species.

Sponges

Sponges inhabit the sea bottom and pose a danger to divers and snorkelers. Sponges are capable of producing both an irritant dermatitis and a contact dermatitis. Sponge irritant dermatitis appears to be due to the sponge spicules, which can become embedded in the host victim. Sponge contact dermatitis, produced by a yet-undefined toxin, leads to local reactions similar to those seen with poison oak. Erythema, pruritus, and vesicles develop with weeping lesions, occasionally leading to desquamation. Local joint swelling and stiffening can occur. Erythema multiforme and anaphylaxis may be a rare complication. The fire sponge,

found in the Florida Keys and Hawaii, often produces a contact dermatitis.

Contact with a sponge may lead to elements of both kinds of dermatitis, and treatment should be initiated accordingly. To prevent the irritant dermatitis, spicules should be removed with adhesive tape and the area bathed in vinegar. The immediate management of sponge contact dermatitis includes immersing the wound site in a vinegar solution. Later therapy relies on the use of local steroid creams and lotions. Systemic steroid therapy may be necessary for severe reactions.

Sea Urchins

Sea urchins are small, nonaggressive animals found on beaches, hiding in coral reefs, or along the ocean bottom. Sea urchin spines are of two types: they may be dangerously sharp, hollow, and toxin-containing, or they may be short, blunt-edged, and nonvenomous. Some species of urchins may have venomous, triple-jawed pincers capable of envenoming and adhering to the victim. Sea urchin venom contains serotonin, steroid glycosides, and acetylcholine-like agents. With direct contact, spines of the urchin can rapidly embed in a victim, producing severe burning dysesthesia with swelling. The envenoming triple-jawed pincers tend to produce more systemic reactions than the sharp, venom-containing spines, leading to edema and hemorrhage at the wound site, paresthesias, paralysis, respiratory failure, and, in rare cases, fatality.

The treatment of wounds due to encounters with sea urchins is primarily of a supportive nature. Bathing the area in hot water to tolerance can help to alleviate the pain. It is important to remove any attached pincerlike organs, as they can continue to envenom the victim when torn from the sea urchin shell. Experts agree that removing the thick calcium carbonate spines is warranted, as these may produce foreign-body granulomas and secondary infections. If easily accessible, smaller, thin, venomous spines can be removed but should otherwise be left to become resorbed. Extracting the spines is not easy, as they can fractionate in the skin. A purplish discoloration of the skin may develop due to the sea urchin dye. Surgical removal of spines using an operative microscope is necessary in instances where spines have lodged in a joint or near a nerve. X-ray films may be helpful in locating spines in the soft tissue. Antibiotic therapy is similar to that for coral cuts.

Stingrays

Stingrays account for hundreds of marine envenomations yearly in the United States. Preferring shallow, warm waters, stingrays common to North America inhabit inlets, reef areas, and river mouths, as well as fresh or brackish water. When an unwitting bather steps on the fish, the stingray reflexly lashes out its tail, on which it carries its stinging spine, and buries the barb into its victim's skin. The spine contains retroserrate teeth and grooves holding venomous glands and is surrounded by an integumentary sheath. The stingray causes a puncture or jagged laceration with its stinger as it releases venom into a victim. Both trauma and envenomation play a role in a stingray wound, and because the wound site contains the stinger as well as pieces of the integumentary sheath, secondary infections are common.

Stingray wounds are most often found on the lower extremities but are occasionally reported on the abdomen and thorax. A patient will initially experience a localized burning pain that peaks in a few hours, resolving over a two-day period. There is localized swelling and bleeding; the sting site ultimately becomes reddened and hemorrhagic. Stingray venom contains 5′-nucleotidase, serotonin, and phosphodiesterase, which cause such systemic reactions as severe muscle cramps, nausea, vomiting, diaphoresis, tachycardia, and cardiac arrhythmias with hypotension, loss of consciousness, and, rarely, death.

TABLE 2.—*Treatment of Stingray Injuries*

Irrigate with normal saline solution, fresh or sea water
Transport to a local care center
Immerse in hot water (45°C to 50°C) for 90 minutes
Debride
Use analgesics for pain relief
Use prophylactic antibiotics
Administer tetanus prophylaxis

Treatment should be initiated as described in Table 2. Stingray injuries should be promptly irrigated; if a normal saline solution or fresh water is not readily available, seawater is an effective alternative to help remove the venom. Stingray wounds can be serious and life-threatening and generally require evaluation at a health care center. Some authorities recommend that, in cases where envenomation is severe and transportation to a local medical facility is delayed, consideration be given to using a proximal lymphatic occlusive bandage. Hot-water immersion at 45°C to 50°C (113°F to 122°F) for 90 minutes should be initiated as soon as feasible; this therapy will inactivate many heat-labile marine toxins and provide local relief. Many authorities report that effective analgesia can be attained with the administration of local anesthetics without vasoconstrictors. The wound should be explored and debrided, with removal of all remnants of the spine and integumentary sheath. Extremity wounds should be elevated. Large abdominal or thoracic cavity wounds require surgical exploration and evaluation. Wound sites may be left packed open or closed loosely with effective drainage. There is anecdotally a high incidence of secondary infection. Although prophylactic antibiotic use remains controversial, most authorities recommend prophylaxis. Appropriate aerobic and anaerobic cultures of all infected wound sites should be done. The initial empiric antibiotic recommendations are directed at treating such organisms as *Vibrio, Alteromonas,* and *Aeromonas* species, with the use of agents such as trimethoprim-sulfamethoxazole, aminoglycoside antibiotics, or ceftazidime until culture and sensitivity results are known. Tetanus prophylaxis should be administered.

Catfish

Catfish, which are found in both fresh and salt waters of North America, puncture and sting victims with sharp spines on their dorsal and pectoral fins. Pain is immediate and often intense, although usually less severe than that induced by stingrays. Initially a victim experiences sharp, shooting dysesthesia at the wound site, with pain extending through the length of the involved extremity. Tissue ischemia can follow, with cyanosis, swelling, and peripheral erythema developing later. Muscle spasms can occur, but severe systemic reactions, including peripheral neuropathy, hypotension, and loss of consciousness, are uncommon.

Most catfish stings occur on the upper extremity when the fish is handled incorrectly; fishers are often victims. It is advisable for persons catching catfish to handle the fish with heavy gloves or a towel. The treatment of a catfish sting is similar to that for a stingray envenomation, with irrigation, cleansing, and the use of hot-water immersion. Systemic symptoms tend to be less pronounced with catfish venom.

Lionfish, Scorpion Fish, and Stonefish

The lionfish, scorpion fish, and stonefish all have in common the ability to envenom using the spines of their dorsal, pectoral, and anal fins. These fish are noted for camouflage and inhabit the Florida Keys, the Gulf of Mexico, Hawaii, and the southern California coast. The lionfish is regularly imported from the Philippines into the United States for purchase by tropical aquarium enthusiasts. Even when dead, this fish can retain active venom for as long as 48 hours and be a source of danger to handlers.

The severity of stings depends on the envenoming species, with the stonefish being the most venomous. The pain of an envenomation with all three of these fish is throbbing and intense, with pallor initially at the puncture wound site, followed by cyanosis and swelling. Systemic symptoms include gastrointestinal discomfort with nausea, vomiting, and diarrhea; neurologic complications with seizures, paralysis, neuropathy, and delirium; and cardiovascular effects with arrhythmias, hypertension or hypotension, congestive heart failure, and death. Secondary infections can occur.

The treatment of envenomating stings is similar to that of stingray stings, using hot-water immersion, irrigation, and wound cleansing. Tetanus prophylaxis is indicated. For severe stonefish envenomations, an antivenom is manufactured by Commonwealth Serum Laboratories of Melbourne, Australia, and is available through San Diego's Sea World, San Francisco's Steinhart Aquarium, or at Sea World of Ohio. This antivenom can be used for stings due to other members of the scorpion fish family but is usually unnecessary with these milder stings.

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Commentary

Why It's Time for a National Health Program in the United States

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The United States lacks a coherent national health program. Current programs leave major gaps in coverage and recently have become more restrictive. Influential policies that have failed to correct crucial problems of the health-care system include competitive strategies, corporate intervention, and public-sector cutbacks with bureaucratic expansion. A national health program that combines elements of national health insurance and a national health service is a policy that would help solve current health-care problems. Previous proposals for national health insurance contained weaknesses that would need correction under a national program. Based on the experiences of other economically advanced countries, a national health program could provide universal entitlement to health care while controlling costs and improving the health-care system through structural reorganization. Current proposals for a national health program contain several basic principles dealing with the scope of services, copayments, financing, cost controls, physician and professional associations, personnel and distribution, prevention, and participation in policy making. Support for a national health program is growing rapidly. Such a program would help protect all people who live in this country from unnecessary illness, suffering, and early death.

(Waitzkin H: Why it's time for a national health program in the United States. West J Med 1989 Jan; 150:101-107)

The United States and the Republic of South Africa are the only two economically developed countries in the world without a national policy that accepts the principle of universal entitlement to basic medical care.[1] Since the 1920s, proposals for a national health program (NHP) have appeared and later have faded from view.[2-7] Many observers believe, however, that our current health-care problems have become intolerable, especially given our nation's wealth, and that piecemeal reforms no longer are suitable approaches to solving these problems.

In this article, I describe the major deficiencies of US health care and the limitations of current health policies. I argue that an NHP would help correct our present difficulties and that it would likely do so with lower costs and less restriction on physicians' and patients' freedoms than the policies we have now.

Gaps in Public Coverage

The enactment of Medicaid and Medicare in 1965 improved the accessibility of services for the poor and elderly, but major problems have remained.[8-11] The provisions of Medicaid vary by state. Federal Medicaid payments go to only limited categories of the poor. Historically, Medicaid has excluded about a third of US citizens with incomes below the poverty level.[12] On the average, Medicare has paid approximately 44% of elderly people's medical expenses.[13]

While Medicaid and Medicare never have covered all people in need, barriers to access have increased markedly during the 1980s. More than 35 million people in the United States are uninsured for at least part of the year.[11] The percentage of poor citizens covered by Medicaid has decreased from 65% in 1976 to 46% in 1984.[14] Access to physician care for persons who are poor, black, and uninsured has declined markedly since 1982.[15] Employed people and their dependents comprise approximately three quarters of those in the United States who are uninsured; more than half of the employed uninsured live in middle-income or high-income households.[16] Working-age persons with private insurance face deductible provisions and limited coverage that frequently create major financial difficulties, as well as frustrating complexities in obtaining benefits.[17]

Because there is no universal entitlement to basic health care, the availability, quality, and utilization of services depend on local conditions. In some geographic regions, there is a surplus of health professionals; in others, a shortage. Access differs according to patients' personal finances, initiative, and linguistic abilities. Mechanisms to assure quality of care are insufficient, and malpractice litigation is extensive. There is also a widely perceived waste of resources in health care. Unnecessary and inefficient services consume a substantial part of the nation's health-care expenditures. In different localities, the occurrence of expensive medical procedures varies widely, again indicating wasteful practice patterns.[18] A laissez faire approach to planning and organization

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ABBREVIATIONS USED IN TEXT

DRG = diagnosis-related group
NHI = national health insurance
NHP = national health program
NHS = national health service

has created a situation where very high quality medicine is available for part of the population, while others cannot receive the most basic services. Patients frequently feel a lack of personal empowerment as they face the frustrations of high costs, complex administrative procedures, inaccessible services, and variable quality.

During the 1980s, in addition to federal cutbacks, states and counties also have reduced publicly supported services. These changes have exerted detrimental effects on many patients' health.[19,20] Statistics cannot adequately convey the emotional and physical impact of restrictive policies on the lives of patients and practitioners.[21] Even when they want to care for indigent patients, practitioners frequently cannot arrange for needed hospital admission, diagnostic procedures, or treatments when patients are uninsured or underinsured. (Table 1 presents a brief list of such typically difficult problems.) It is hard to justify the suffering of such patients, when appropriate treatment is available and when we live in a country with abundant economic resources.

TABLE 1.—*Financial Barriers to Care at an Academic Medical Center—Selected Case Summaries, 1985-1988**

US Citizens Suffering From Cutbacks and Increased Copayments Under Medi-Cal (California's Medicaid Program)

- A 31-year-old man with severe unilateral headaches could not afford a computed tomographic (CT) scan of the head because his monthly deductible under Medi-Cal increased from $50 to $250; he later was brought delirious to the emergency room, where an emergency CT scan revealed a brain tumor with poor prognosis.
- A 56-year-old man with metastatic soft-tissue sarcoma could not afford follow-up visits, medications, visiting nurse, or hospice because his deductible under Medi-Cal had increased to $350 per month.

US Citizens Facing Restrictions Due to Policies of County-Administered Medically Indigent Adult (MIA) Program

- A 63-year-old man with hypertension, renal insufficiency, and prostatic hypertrophy could not gain approval from the county's MIA program under Medi-Cal for a prostatectomy; his urinary retention and renal function gradually worsened; when he finally required dialysis, he became eligible for Medicare.
- A 29-year-old woman presented with a breast mass; mammography was consistent with cancer; approval of MIA funding for outpatient biopsy was delayed for nearly 1 month during the eligibility screening process because the condition was not considered an emergency.
- A 44-year-old man had malignant melanoma, confirmed by a limited biopsy with incomplete excision; outpatient surgery for wider resection was delayed for three months by MIA eligibility procedures.
- A 52-year-old man developed unstable angina after a myocardial infarction; the MIA program disapproved funding for coronary angiography.

Undocumented Immigrants

- A 22-year-old woman from Costa Rica without legal documents presented with sickle cell anemia, cardiac enlargement, and a right axillary mass; for 2 months, arrangements could not be made for an echocardiogram or biopsy of the mass; as a result, the patient moved to another county in California with less restrictive policies about medical care for the undocumented.
- A 31-year-old undocumented man from Mexico presented with carpal tunnel syndrome of his right hand that interfered with his work as a tailor; acromegaly associated with a pituitary tumor was diagnosed, but radiation therapy or neurosurgery could not be arranged because of financial impediments; after waiting nearly three months, the patient was lost to follow-up when he returned to Mexico.

*From case reports of patients with financial barriers to care, University of California, Irvine, Medical Center, Irvine, California.

Policies That Don't Work

Current health policies in the United States have created a patchwork of programs that leave major gaps in coverage. Policy goals are imprecisely defined, and policy implementation is often erratic and contradictory. Several unsuccessful policies illustrate this theme.

The Failure of Competitive Strategies

During the early 1980s, competitive strategies attracted prominence in health-policy circles. A series of proposals to foster competition among providers, and thus to lower costs, gained wide attention.[22-24]

Competitive strategies in health care now have received major criticism.[24-26] Medical services never have shown the characteristics of a competitive market. Government pays for more than 40% of health care. The insurance industry, pharmaceutical industry, and medical equipment manufacturers all manifest monopolistic tendencies that inhibit competition. Hospitals and physicians wield political-economic power through professional organizations that reduce the impact of competitive strategies. Physicians also affect the demand for services, through recommendations about referrals, diagnostic studies, and treatment. Analytically, the effects of competition on costs are difficult to separate from other important changes, especially the general slowing of inflation, the requirement of major copayments by patients, and the impact of prepayment.[24] Despite policies favoring competition, overall health-care costs have continued to rise faster than the general rate of inflation.

At the practical level, competitive strategies have led to major dislocations and gaps in services. For example, competitive contracting and prospective reimbursement under Medi-Cal (California's Medicaid system) have worsened the financial crises of hospitals with a large proportion of indigent clients. As a result, the California legislature has enacted a series of "bail-out" measures designed to ease these institutions' difficulties.[27,28] Moreover, by disrupting services, the new Medi-Cal policies have led to a measurable worsening of some patients' medical conditions.[19,20] In other states, competitive health plans have suffered severe and unpredicted financial problems, and patients have encountered major barriers to access, including direct refusal of care by providers.[29-31] In short, competitive strategies have exacerbated the difficulties of maldistributed and inaccessible services.

Corporate Penetration of Health Care

Current policies encourage corporate expansion in the medical field. By the mid-1970s, private insurance companies, pharmaceutical firms, and medical equipment manufacturers already had achieved lucrative positions in the medical marketplace.[32-35] In the 1980s, multinational corporations have taken over community hospitals in all regions of the country, have acquired and/or managed many public hospitals, have bought or built teaching hospitals affiliated with medical schools, and have gained control of ambulatory care organizations.[3,36-38]

Despite concerns about cost containment, corporate profitability in health care has encountered few obstacles.

For the past five years, after-tax profits for corporations with activities in health care have ranked the second highest among US industrial groups ("Annual Report on American Industry," *Forbes,* January 12, 1987, p 258). Nationally, for-profit chains control about 15% of all hospitals, but in some states (for example, California, Florida, Tennessee, and Texas) the chains operate between a third and half of hospitals. Ownership of nursing homes by corporate chains has increased by more than 30%.[39] For-profit corporations have enrolled about 70% of all health maintenance organization subscribers throughout the country. Between 1981 and 1983, the number of corporate-owned home health agencies tripled, far outstripping those operated by visiting nurse associations, hospitals, skilled nursing homes, and other nonprofit agencies.[39] Ironically, despite the rhetoric of competition, monopolization in the health sector is occurring rapidly, as a limited number of large corporations and insurance companies dominate the market and smaller health-care institutions cannot compete successfully.

While enthusiasts perceive several economic advantages of corporate involvement in health care, the substantiation of such claims is quite limited. For example, it is argued that tough-minded managerial techniques will increase efficiency and decrease costs, although several studies have shown that for-profit health-care organizations are no more efficient than nonprofit ones.[40,41] Similarly, research on corporate management has not supported the claim that corporate takeover can alleviate the financial problems of hospitals serving indigent clients.[42] Corporations appear to offer a source of capital that is difficult to obtain from public or philanthropic sources. However, economic analysts have predicted that the financial strength of health-care corporations will decline as a result of prospective reimbursement policies and other restrictions on hospital admissions, prior pricing and markup practices, and the use of ancillary services.[40,43] Such concerns have contributed to worsened profit margins and stock market performance for several corporate chains. Some corporations have laid off staff members and have initiated rigorous productivity standards, leading to insecurity and dissatisfaction for physicians, nurses, and other employees.[44]

Corporate involvement in health care also has raised major ethical problems. There is growing concern that corporate strategies lead to reduced services for the poor. While some corporations have established endowments for indigent care, the ability of such funds to assure long-term access is doubtful, especially when cutbacks occur in public-sector support.[45,46] Other ethical concerns have focused on physicians' conflicting loyalties to patients versus corporations, the unwillingness of for-profit hospitals to provide unprofitable but needed services, and similar issues.[36,37] These observations raise further doubts about the wisdom of policies that encourage corporate penetration of health care.

Public-Sector Programmatic Cutbacks and Bureaucratic Expansion

Recent policies have greatly reduced public-sector health programs. Cutbacks have occurred in the national Medicaid program; Medicare; block grants for maternal and child health, migrant health services, community health centers, and birth control services; health planning; educational assistance for medical students and residents (affecting especially minority recruitment); the National Health Service Corps; the Indian Health Service; and the National Institute of Occupational Safety and Health. Many federally sponsored research programs also have been cut.

During this same time period, measures of health and well-being in the United States have either stopped improving or actually have become worse. For example, the recent halt in the rate of decline in infant mortality coincides with cutbacks in federal prenatal and perinatal programs; in several low-income urban areas, infant mortality has increased.[47] Among blacks, the high postneonatal and maternal mortality rates have not fallen during the past five years, after decades of steady decline, and a growing proportion of black women have not been able to receive adequate prenatal care.[48-50] These reversals in health status and health services, emerging as direct manifestations of changes in federal policies, are unique among economically developed countries.

Alongside these programmatic cutbacks, bureaucratization and regulation in the health-care system have grown rapidly.[51,52] The ironic distinction between the rhetoric of reduced government, versus the reality of greater government intervention, is nowhere clearer than in the Medicare diagnosis-related group (DRG) program. Intended as a cost-control device, DRGs have introduced unprecedented complexity and bureaucratic regulation. By providing reimbursement to hospitals at a fixed rate for specific diagnoses, DRGs encourage hospitals to limit the length of stay, as well as services provided during hospitalization. Hospitals have responded to DRG regulations with an expansion of their own bureaucratic staffs and data-processing operations, more intensive utilization review, and a tendency to discharge patients with unstable conditions when DRG payments are exhausted. Private hospitals admitting a small proportion of indigent patients have profited under DRGs; public and university hospitals that serve a higher percentage of indigent and multiproblem patients face an unfavorable case mix within specific DRGs and thus have fared poorly.[53,54] The extensive utilization review that DRGs have encouraged in hospitals has focused on cost cutting, rather than assuring quality of care. Moreover, DRGs' contribution to cost controls remains unclear, in comparison to other factors such as reduced inflation in the economy as a whole. Despite recent proposals for catastrophic coverage, Medicare copayments required from the elderly have continued to rise. Overall, DRGs have increased bureaucratic complexity, while federal support for direct health services has declined.

The Need for a New Policy Direction

In short, current policies do not adequately address basic problems of health care in the United States, and the results are very unpleasant. A new and more basic approach to organizing the health-care system is the best way to deal with these gaps in public services and the failure of previous policies.

A National Health Program for the United States

A national health program, including elements of national health insurance (NHI) and a national health service (NHS), could help solve the problems that we face. National health insurance is a national program that provides public financing of health care for a country's population. An NHS goes beyond public insurance to create a different organizational structure whose intent is to construct a coordinated system of care.

Weaknesses of Prior Proposals for National Health Insurance

During the late 1970s, the US Congress considered at least 18 separate proposals for NHI. The supporters of these measures ranged across a wide political spectrum, including the Nixon administration, the American Medical Association, and both liberal and conservative legislators. When the Reagan administration took power in 1981, a policy of cutbacks in health and welfare programs eliminated the possibility that NHI could be enacted in the near future.

Within the range of NHI proposals considered during the late 1970s, several fundamental problems became clear. First, NHI would have changed payment mechanisms, rather than the organization of the health-care system. Under these proposals, the federal government would have guaranteed payment for most health services. However, NHI would not have assured that practitioners would work in different ways, in different areas, or with different patients.[55(pp 218-220)]

Most plans for NHI would not have covered all needed medical services. Coinsurance provisions would have required out-of-pocket payment for some fixed percentage of health spending. Under coinsurance, an individual or family pays the initial costs up to a specified amount before NHI takes over. While such copayments may have helped control costs, coinsurance predictably would have a detrimental impact on the poor and other vulnerable groups.[56]

New and compulsory taxation, usually as fixed payroll deductions, would have paid for NHI. The financing arrangements for NHI therefore would have been regressive; that is, low-income people would have paid a proportionately higher part of their income for health care than would the wealthy. Although various tax mechanisms could relieve the burden of health insurance for low-income patients, legislators have devoted little attention to this issue.[57]

In most NHI plans, private insurance companies would have served as the fiscal intermediaries for NHI. They would have received compensation for distributing NHI payments from the government to health providers. Such provisions thus would have assured continued profits for the private insurance industry.

Regarding accessibility, NHI proposals would have contained few provisions for improving geographical maldistribution of health professionals. Fee schedules might have been higher in some proposals for doctors who practiced in underserved areas, but such incentives could not assure that physicians actually would work in these areas.[55(pp 218-220)]

Perspectives From Other Countries

Planning for an NHP in the United States would require open-minded consideration of the strengths and weaknesses of existing NHI plans and NHSs around the world. For instance, most countries in Western Europe and Scandinavia have initiated NHS structures, permitting private practice in addition to a strong public sector.[1,58,59] Canada has achieved universal entitlement to health care through an NHI program that depends on private practitioners, private hospitals, and strong planning and coordinating roles for the national and provincial governments.[60-64]

NHPs vary widely in the degree to which the national government employs health professionals and owns health institutions. For example, the NHPs of Great Britain, Denmark, and the Netherlands contract with self-employed general practitioners for primary care; Canadian private practitioners receive insurance payments mainly on a fee-for-service basis; in Finland and Sweden, a high proportion of practicing doctors work as salaried employees of government agencies. In Great Britain the national government owns most hospitals; regional or local governments own many hospitals in Sweden, Finland, and other Scandinavian countries; and Canada's system depends on governmental budgeting for both public and private hospitals. Even in Britain, whose NHS has received wide critical attention, the NHS continues to command support from the majority of physicians and the general public.[65,66] Throughout the world, there is a growing trend toward the establishment of NHPs, based on universal entitlement to care.[58]

The Canadian system is very pertinent to the United States, because of geographical proximity and cultural similarity.[60-64] Canada assures universal entitlement to health services through a combination of national and provincial insurance programs. Doctors generally receive public insurance payments through fee-for-service arrangements. Hospitals obtain public funds through prospectively negotiated contracts, eliminating the need to bill for specific services. Progressive taxation finances the Canadian system, and the private insurance industry does not play a major role in the program's administration. Most Canadian provinces have initiated policies that aim to correct remaining problems of access based on geographic maldistribution. Cost controls in Canada depend on contracted global budgeting with hospitals, limitations on reimbursements to practitioners (the latter policy remains controversial for physicians in some provinces), and markedly lower administrative expenses because of reduced eligibility, billing, and collection procedures. Regarding administrative efficiency (which has drawn criticism in the NHPs of Britain and some Eastern European countries), observers of the Canadian NHP have noted efficient procedures and an overall reduction of administrative personnel, compared to the United States.

Because of the commonly expressed concern about costs in the United States, the experiences of existing NHPs are instructive. The costs of US health care already are quite high, accounting for approximately 11% of the gross national product, a larger percentage than in Canada or any European country with an NHP.[60] It is often presumed that an NHP with expanded entitlement to services would increase US health-care costs and add to the federal budget deficit.

However, the presumption that an NHP would increase costs is not necessarily correct; depending on how an NHP is organized, costs might well fall to below their current level. First of all, a major savings would come from reduced administrative overhead for billing, collection procedures, eligibility determinations, and other bureaucratic functions that no longer would be necessary. In the Canadian NHP, for instance, global budgeting for hospitals has greatly reduced administrative costs, and a much smaller role for the private insurance industry has lowered costs even further by restricting corporate profit.[60,62]

Recent analyses have shown that cost savings under an NHP from reduced administrative functions and entrepreneurialism could total more than $40 billion annually. Administrative cost savings would derive chiefly from reductions in insurance overhead, physicians' overhead, hospital administration, and nursing home administration, while restrictions on profit would affect the private insurance industry, pharmaceutical companies, medical equipment

firms, and for-profit chains.[51,67] These savings, resulting partly from a reduction in wasteful procedures, could occur even if private practice continued within the NHP, as it does in Britain, Canada, and many other countries, and even if physicians' incomes remained at their present levels. Countries with publicly organized NHPs have provided universal entitlement to health-care services while controlling costs far more successfully than has been possible in the United States.[68]

Principles and Prospects for a US National Health Program

The fundamental assumption of an NHP is that universal entitlement to adequate health care is a basic human right. Thus, the NHP would strive toward equity in the availability of services, across geographic boundaries and income differentials. Since the mid-1970s, planners have worked with members of Congress and other prominent politicians in drafting NHP proposals (see Dellums and colleagues,[69] Roybal,[70] Jackson,[71] and the Working Group on Program Design of Physicians for a National Health Program[72]). Taken together, these plans include a number of basic principles for an NHP:

- The NHP would provide for comprehensive care, including diagnostic, therapeutic, preventive, rehabilitative, environmental, and occupational health services, dental and eye care, transportation to medical facilities, social work, and counseling.
- These services would not require out-of-pocket payments at the "point of delivery." While carefully limited copayments for certain services may be appropriate (as in Canada[60,63]), the implementation of copayments would assure that they do not become barriers to access.
- Financing for the NHP would come from taxation of individual and corporate income, plus a tax on gifts and estates. Taxation would be progressive, in that individuals and corporations with higher incomes would pay taxes at a higher rate.
- The NHP would reduce administrative costs, private profit, and wasteful procedures in the health-care system. A national commission would establish a generic formulary of approved drugs, devices, equipment, and supplies. A national trust fund would disburse payments to private and public health facilities through global and prospective budgeting. Profit to private insurance companies and other corporations would be closely restricted.
- Professional associations would negotiate the fee structures for health-care practitioners. Financial incentives would encourage cost-control measures through health maintenance organizations, community health centers, and a plurality of practice settings. While the NHP would employ some physicians, especially in underserved areas, practitioners would be free to continue working in private practice and to receive reimbursement from the NHP on a fee-for-service basis.
- To improve geographic maldistribution of health professionals, the NHP would provide free education and training in return for required periods of service by medical graduates in underserved areas.
- The NHP would initiate programs of prevention that would emphasize individual responsibility for health, risk reduction, maternal and infant care, occupational and environmental health, long-term services for the elderly, and other efforts to promote health. One aim of these measures would be to reduce self-destructive and costly behaviors such as alcoholism, smoking, and drug abuse.
- Elected community representatives would work with providers' groups in local advisory councils. These councils would participate in quality assurance efforts, planning, and feedback that would encourage administrative responsiveness to local needs.

These principles would help correct the weaknesses of prior NHI proposals. In addition to guaranteeing payment for services, the NHP would create organizational changes to improve access and to reduce maldistribution. The NHP would provide comprehensive coverage; any copayments would not interfere with access to basic services. Progressive taxation would provide the NHP's financing so that low-income patients would not face additional burdens. Elected representation on local councils would provide a sense of added empowerment for consumers and also probably for providers.

Support for an NHP in the United States is growing rapidly. Public opinion polls consistently have shown that a majority of the US population favors an NHP that assures universal entitlement to basic health-care services.[73,74] The American Public Health Association has passed several resolutions calling for an NHP; sessions concerning an NHP occur regularly at the association's national and regional conventions. The Coalition for a National Health System is a nationwide organization that is coordinating educational and organizing efforts throughout the country. Leaders and members of senior citizens' groups, including the Gray Panthers, the American Association of Retired Persons, the Congress of California Seniors, and similar groups of older people, have taken a very prominent role in working for an NHP. In November 1986, 67% of Massachusetts voters supported a proposal urging the US Congress to enact an NHP, and Massachusetts subsequently enacted a state health program designed to provide universal coverage.[75,76] A ballot initiative on an NHP also has been introduced in the California legislature.[77] Similar efforts are under way in other states to bring the option of an NHP to the voting public. Recent proposals in the US Congress have called for mandatory insurance for all working adults. In addition, the Rainbow Coalition endorsed an NHP during the 1988 Presidential campaign.[71]

Will the medical profession continue to oppose an NHP? At the present time, dissatisfaction is rising among physicians. Practitioners face increased cost controls and bureaucratic obstacles in collecting fees. The conditions of practice have become more constrained, incomes have tended to plateau or even to decline, and individuals entering practice face financial uncertainty. More than half of all physicians now work in salaried positions, often within for-profit organizations that closely regulate productivity. Some observers have claimed that these constraints are creating a "proletarianized" medical profession.[78] Under these circumstances, it is important to note that in Canada, Western Europe, and Scandinavia, despite periodic problems and reorganizations, NHPs now claim wide professional support.[58] Soon after the passage of Medicare and Medicaid, the opinions of US physicians quickly reversed, so that by 1968 a majority of physicians favored these public programs.[79] Predictably, similar changes in professional opinion about an NHP also will occur in the United States. The seeds of these changes are evident in the American Medical Association's proposals for

NHI during the 1970s, the AMA's more recent proposals for a coherent national health policy,[80,81] the wide professional support for catastrophic Medicare coverage, and especially a new and comprehensive proposal by physicians for an NHP.[72]

Strong opposition to an NHP will come from the corporations that currently benefit from the lack of an appropriate national policy: the private insurance industry, pharmaceutical and medical equipment firms, and the for-profit chains. While corporate resistance should not be underestimated, there is also potential support for an NHP from the corporate world. The costs of private-sector medicine have become a major burden to many nonmedical companies that provide health insurance as a fringe benefit to employees. Corporations that do not directly profit from health care have influenced public policy in the direction of cost containment.[82,83] In Western Europe and Scandinavia, corporations have come to look kindly on the cost controls and services that NHPs provide, even when corporate taxation contributes to NHP financing.[58] As the crisis of health-care costs continues to affect US corporations, they too may examine an NHP as a positive option.

Conclusion—The Time for a National Health Program Has Come

We in the United States need and deserve a national program that protects all people who live in this country from unnecessary illness, suffering, and early death. Current health policies have failed. An NHP would provide entitlement to health care as a basic human right. In addition to controlling health-care costs, an NHP would improve the way our system is organized, and it would remove many of the most frustrating features of medical practice. Given the suffering in our midst, can we now aim for anything less?

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NORTH IDAHO. Family Physician needed to join four physician group. College and two state universities within the locality. Area provides abundant outdoor recreational opportunities. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501.

PATHOLOGIST, APCP, desired for aggressive three man group with demanding, busy, interesting practice. Must have or be willing to rapidly develop a forte in Microbiology. Pacific/Rocky Mountain Northwest with abundant outdoor activities and competitive income. Please reply to Number 123, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE/SACRAMENTO. Due to continued growth, positions for Family Practice are now available at Kaiser Permanente Medical Center, south Sacramento. Our salary is very competitive and we have an outstanding retirement and benefits package. Your practice at Kaiser will allow insulation from the headaches and financial uncertainty of private office practice, while fostering your professional growth at a first rate medical center. For further information, please contact Jack Berger, MD, Assistant Chief, Department of Medicine, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823; or call (916) 686-2267.

PHYSICIANS WANTED

OB/GYN. San Francisco bay area prepaid medical group with new LDR suite and family centered Obstetrical practice as well as full Gynecological practice has opening with competitive salary and generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN Department, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063.

GENERAL INTERNISTS. BC/BE General Internists needed for multispecialty group. We are experiencing robust growth and are seeking Internists to join large established Department of Medicine with University affiliation. Our hospital provides integral part of University of California, Davis housestaff training program. Pleasant outpatient practice setting is in six to nine physician modules. Excellent starting salary with rapid early advancement and steady yearly salary growth thereafter. Full benefits and retirement. This is an outstanding practice opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

SACRAMENTO, CALIFORNIA. Family Practitioners and Internists needed part-time for staffing ambulatory care clinic. Our clinic operates seven days a week during days and evenings and provides episodic care on a same-day basis. Physicians may choose to work one to 10 half-days or evenings per week with wide flexibility. Full benefits and retirement if working six or more half-days a week on a steady basis. Please call John Petitt, MD, (916) 973-5560 or send CV to John Petitt, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825.

PHYSICIANS WANTED

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ALL SPECIALTIES

Unlike other search firms, **DAR & Associates'** physician recruiters specialize in physician placements exclusively.

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OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151 ext 294, or 1 (800) 234-1231.

PACIFIC NORTHWEST—INTERNIST. There are three busy solo Internists, practicing near our 155-bed hospital in Tacoma, Washington, who are seeking associates. They prefer candidates with interest in Geriatrics. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-1, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

SONOMA AND LAKE COUNTIES. Immediate openings for Emergency Physicians who desire to live in the wine country north of San Francisco. Prefer BC/BP Emergency Physicians, but will consider BC in Family Practice, Internal Medicine, or Surgery in conjunction with Emergency Medicine experience. Low/moderate volume ED's or in combination with satellite ACC. Guaranteed $90-$100,000 per year; paid malpractice. Contact Richard Gillespie, MD, Redwood Empire EM Group, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

RHEUMATOLOGIST. BC/BE wanted to join solo certified Rheumatologist with group coverage in large southern California private-pay Rheumatology practice. Salary plus bonus with association and investment opportunity. Lab, x-ray, and physical therapy. Clinical research and teaching opportunities. Send CV to R. S. Gordon, MD, FACP, Arthritis Medical Clinic, 5945 Brockton Ave, Riverside, CA 92506; or call (714) 781-7700.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

(Continued on Page 122)

AIM HIGH

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If you're a **Surgeon** or **OB/GYN** or **Other Medical Specialist,** the Air Force may have a special practice for you.

What makes it special? You'll enjoy an excellent pay and benefits package. There'll be more time to spend with your family. You'll receive 30 days of vacation with pay each year. And you will work with modern equipment and some of the most highly trained professionals in the world, serving your country and your patients. Now that's special!

Find out just how special your practice can be. Call

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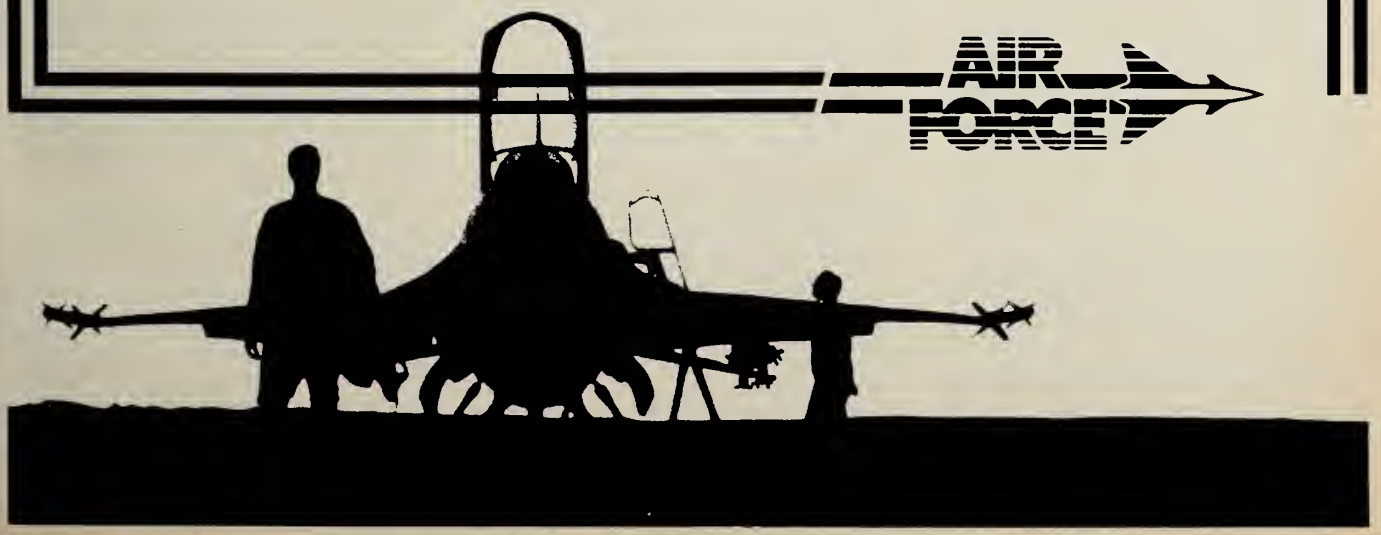
AIR FORCE



(Continued from Page 120)

PHYSICIANS WANTED

ORTHOPAEDIST
Southern California

Orthopaedic Surgeon (Board certified preferred) needed for lucrative, expanding medical practice in Los Angeles area specializing in Worker's Compensation. California license needed as of starting date.

Primarily office practice. Light elective surgical schedule can be limited to arthroscopies.

Virtually no call, evenings or weekends.

Excellent starting salary with possible partnership in less than one year.

Send letter and CV to:

Department WJO
8306 Wilshire Blvd, #7727
Beverly Hills, CA 90211

OCCUPATIONAL/FAMILY PRACTICE. The Pacific Northwest's leading outpatient medical provider has career opportunities for Primary Care Physicians to join an expanding 150 person medical group. Full/part-time openings throughout California and Seattle-Tacoma, Washington. Prior outpatient/occupational experience preferred. Attractive package includes competitive base salary plus incentive program, malpractice insurance, comprehensive benefits, 401(k) plan, vacation/sick/holiday/CME. Opportunity for advancement for energetic, hard-working physician committed to quality health care. Join our dynamic team of health care professionals. Contact Robin Smith, Director, Personnel, Readi-Care/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

FIVE PERSON INTERNAL MEDICINE GROUP seeking BC/BE Pulmonologist, intensive care bronchoscopy training. Sierra Foothills, California. Reply to Number 122, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee for service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

ORTHOPEDIST. One day per week. Medical-legal evaluations for traumatic injury patients. No surgery. California license required. Lucrative fee for service with high growth potential and guaranteed base. Contact Director, PO Box 14046, San Francisco, CA 94114.

PHYSICIANS WANTED

SUN VALLEY—Internist to practice Primary Care with two Internists in quality multispecialty group. Well equipped hospital. High quality of life with outstanding year 'round recreation presents unique opportunity and professional challenge. CV and references with first letter please. Tom Peterson, PO Box 66, Sun Valley, ID 83353-0066; (208) 622-4526.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for two BC/BE Family Practitioners to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4000.

FAMILY PRACTICE, PUGET SOUND. 23 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

INTERNIST, BE/BC—SAN DIEGO to join well established 10 physician Internal Medicine group minutes from hospital. Interest in Geriatric patients. Guaranteed salary with incentive and full benefits leading to full partnership after one year. Send CV to Frank Millward, Administrator, 5111 Garfield St, La Mesa, CA 92041.

FAMILY PRACTICE BC/BE position available immediately in a satellite clinic of a large Seattle area multispecialty group practice. Diverse patient population including managed care, retired military, and fee-for-service. Attractive salary and benefits. Contact Connie J. Smith, MD, Pacific Medical Clinic-Bellevue, 14730 N.E. 8th St, Bellevue, WA 98007; (206) 644-9533.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural lifestyles. Contact Dr Donn Cobb, Health Officer, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

PEDIATRICIAN. County-sponsored, 17 physician multispecialty group practice with three satellite locations is looking for a BC/BE Pediatrician to provide primary and preventive health care services. Committed to high quality care. Comprehensive benefit package includes malpractice insurance coverage. Consider a semi-rural lifestyle with cultural amenities; easy access to metropolitan areas, the Sierra Nevadas, and the Pacific Ocean; lower housing costs (median price $75,000); and excellent schools. Salary: $76,536-$93,365 annually. Send CV to Michael L. MacLean, MD, Hillman Health Center, 1062 S. "K" St, Tulare, CA 93274; (209) 688-2015. Equal Opportunity Employer.

WASHINGTON. General Internist BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is composed of 32 physician multispecialty group. Guaranteed income, plus excellent benefits. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

PEDIATRICIAN OR PEDIATRICIAN/NEONATOLOGIST. Multispecialty medical group seeks full-time BC/BE Pediatrician or Pediatrician/Neonatologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

OBSTETRICIAN/GYNECOLOGIST. Multispecialty medical group seeks full-time BC/BE Obstetrician/Gynecologist to join four other specialists. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

EUGENE, OREGON. Family Physicians, BE/BC, sought to join growing 36 Physician Family Practice/Internal Medicine group in Eugene and nearby rural Cottage Grove. OB optional. Excellent OB support available. Initial income guarantee with incentive. Partnership anticipated after two years. Outstanding schools. Abundant cultural and recreational opportunities. Please send CV or call Rob Daugherty, MD, Oregon Medical Group, 78-A Centennial Loop, Eugene, OR 97401; (503) 688-9140.

CALIFORNIA, NORTHERN. A stable group of four ABEM Certified/Eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

INTERNAL MEDICINE DEPARTMENT CHAIRMAN. Maricopa Medical Center of Phoenix, Arizona, is seeking a chairman for its Department of Internal Medicine. We seek a well-qualified individual with recognized credentials in medical education, patient care, and research. Vigorous leadership abilities are required. Duties will include active supervision of the residency and fellowship training programs. The candidate must be BC in Internal Medicine. Maricopa Medical Center is an Equal Opportunity Employer. Those interested should submit inquiries and CV to J. Kipp Charlton, MD, Chairman, Medicine Chairman Search Committee, Maricopa Medical Center, PO Box 5099, Phoenix, AZ 85010.

WOFFORD HEIGHTS (FAMILY PRACTICE). Fantastic opportunity for the right Physician! New 7,000 square foot multispecialty clinic opening in January 1989. Located in the beautiful mountain lakeside resort community of Wofford Heights, California, an hour east of Bakersfield, this facility will have office and exam space for four Physicians. Included will be a Pharmacy, full lab, x-ray services. Excellent salary and benefit package. No investment by the Physician. Malpractice paid in full. This is a rare opportunity to combine a very attractive lifestyle and an excellent practice opportunity. We are seeking to contract four Physicians now. Call George Johnston, (805) 845-3731 for details or write PO Box 457, Lamont, CA 93241.

SEATTLE, WASHINGTON (north Seattle, Shoreline/Richmond beach areas). Family Practice Group of five Family Practitioners (two women and three men), all BC, looking for part-time/full-time BC Family Practitioner. Includes flexible OB and General Medical call coverage. Excellent staff and congenial atmosphere. Guaranteed salary with excellent benefits plus opportunity to join practice after one year. Send CV to Barbara Derry, Administrator, Highland Clinic PS Inc, 18514 Firlands Way N, Seattle, WA 98133; (206) 542-4848.

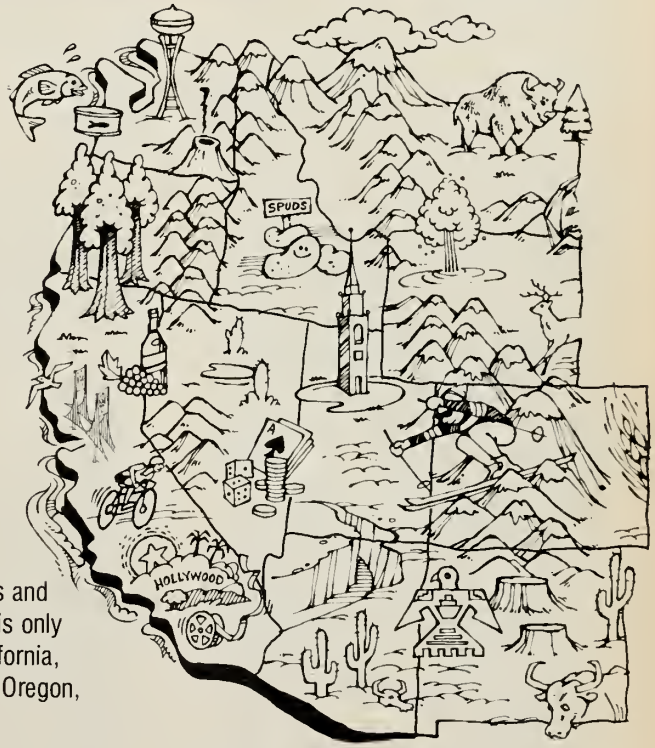
(Continued on Page 124)

The Western Journal of Medicine

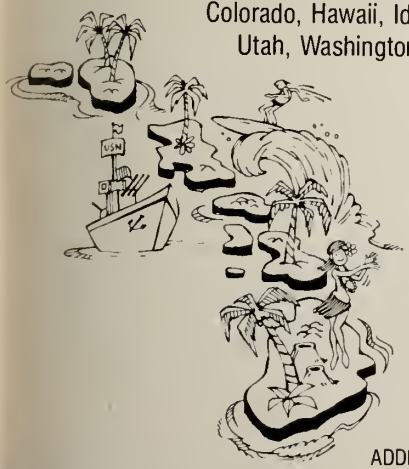
Medical Student 1989 Writing Award Competition

$1,000 CASH PRIZE!

■ Enter your original medical research or medical review article—the article must be of interest to clinicians and not previously published. The winner will receive a $1,000 cash prize and a two-year subscription to **The Western Journal of Medicine.** The winning article will be published in **WJM. Deadline to enter February 1, 1989.**



■ **WJM** is the official journal of eight western state medical associations and six clinical investigation/specialty societies. This competition open is only to medical students attending school in Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, or Wyoming.



■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

ADDITIONAL RULES:

■ Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for consideration for this award.

■ Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally among the co-authors.

■ Articles must conform to **WJM's** style—our style guide, "Information for Authors," appears in the January and July issues, or you may write our editorial department for a copy of the guide.

■ Articles will be judged by the editors and the editorial and advisory boards of the journal.

■ The winner will be announced and the article published in **WJM.** In case of a tie, the $1,000 award will be divided equally.

DEADLINE: FEBRUARY 1, 1989.

For additional information write to:

THE WESTERN JOURNAL OF MEDICINE
Editorial Office/Award Competition
P.O. Box 7602
San Francisco, CA 94120-7602

(Continued from Page 122)

PHYSICIANS WANTED

JAPANESE SPEAKING PHYSICIANS
Up to 150K+

Fortune 500 companies are seeking Japanese speaking bilingual physicians. Opportunity to develop own practice. Co. offers free office space, malpractice insurance plus guaranteed salary. Positions available in Ohio and Michigan. Out-of-state candidates will be relocated.

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725 S. Figueroa St, Ste 3100
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Doug Versteeg (213) 955-4942
Junko Kanke (213) 955-4923

MENDOCINO COUNTY. Only Internist in rural service area of 10,000 seeks BE/BC associate. 150 miles north of San Francisco. Goal: quality medicine, expanded personal life. Contact Bruce Andich, 88 Madrone, Willits, CA 95490 or (707) 459-6115.

MEDICAL DIRECTOR—CHINESE HEALTH SERVICES. $4,117 per month. The licensed Doctor of Osteopathy will develop, implement, and supervise an Osteopathic Acute Care and medical center's program to provide health care services (Osteopathic) to a large, metropolitan Chinese community. Prepare and present bilingual (Chinese and English) health care forums and prepare bilingual educational materials. Provide medical services to and communicate with Chinese patients unable to understand English. Be available for house calls and urgent care coverage. Participate in hospital activities such as medical staff committees (i.e., Pharmacy and Therapeutic Committee, Infection Control Committee, General Practice Department, etc). Applicants are required to have a degree in Osteopathic Medicine which shall include the one year of Osteopathic rotating internship, be qualified for licensure in the State of Arizona, have patient care experience, have complete bilingual, Chinese (Cantonese) and English skills, and have teaching and public speaking skills. Résumés must be received not later than 20 days from the date of initial publication. Qualified applicants send résumé or application letter to AZ DES Job Service, Attn: 732-A Re: 0802635, PO Box 6123, Phoenix, AZ 85004 (Job location: Emp pd ad; Proof of authorization to work in U.S. will be required upon hire).

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a southern California teaching hospital affiliated with UCLA and UCI School of Medicine, seeks an Associate in the Division of Pediatrics/Department of Family Medicine. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching, and qualifications for faculty appointment in UCLA Department of Pediatrics. Compensation and benefits are competitive. A part-time private practice is permitted. Please reply with CV to Navin Amin, MD, Chairman, Kern Medical Center, Department of Family Medicine/Pediatrics, 1830 Flower St, Bakersfield, CA 93305, or telephone (collect) at (805) 326-2192.

SALT LAKE CITY OB/GYN. Due to retirement, immediate opportunity for OB/GYN in established practice in one of Salt Lake City's large multispecialty clinics. Suburban location. Call Administrator at (801) 486-6941 or send CV to 2000 South 900 East, Salt Lake City, UT 84105.

FAMILY PRACTICE. Phoenix, Arizona BC/BE private practice, no OB. In-office lab and x-ray. Growing area, southwestern life style at its best. Located across from modern, full-service hospital. Call (602) 846-7500 or résumé to Westside Family Practice, 5251 W. Campbell Ave, #105, Phoenix, AZ 85031.

PHYSICIANS WANTED

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

PULMONOLOGIST. Pulmonologist wanted as associate in very busy Pulmonary/Critical Care practice in Kern County, California. Practice is 100 percent Pulmonary/Critical Care and includes Pulmonary Consultation, Pulmonary Physiology Laboratory, Pulmonary Rehabilitation, Respiratory Care, state-of-the-art Sleep Lab available. Excellent opportunity for BC/BE Pulmonologist looking for potential partnership. Those interested please send CV and inquiries to Dale T. Herriott, MD, Inc, 2525 Eye St, Ste 2B, Bakersfield, CA 93301.

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Parkway, San Jose, CA 95119; (408) 972-6180.

PEDIATRICIAN to join a busy practice. Hospital three miles from office. Excellent central location, between Fresno and Bakersfield. Friendly growing rural community with many cultural and recreational activities available. Send CV to J. Bakhoum, MD, 660 E. Visalia Rd, Farmersville, CA 93223; (209) 594-5892.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; telephone 1 (800) 544-1987.

INTERNIST. The Visalia Medical Clinic has an opening for a BC/BE General Internist. The Clinic is a 43 physician multispecialty group located in the San Joaquin Valley and central California. Medicine Department consists of five General Internists, along with subspecialties in Cardiology, Endocrinology, Gastroenterology, Medical Oncology and Hematology, Pulmonary Medicine, and also Neurology. Visalia is a progressive city of 65,000 people, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, or Robert A. Havard, Jr, MD, Dept of Internal Medicine, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

Ads Get Results!

ADVERTISING INFORMATION

(415) 541-0900, Ext 376

PHYSICIANS WANTED

Physicians wanted for leading clinic

Prestigious Chicago-based clinic group specializing in the treatment of venous disorders is expanding nationally. Our newest clinics in Los Angeles, San Diego and San Francisco are in need of physicians trained in internal medicine—or who have a broad base of medical experience. We will provide complete training in the latest proprietary techniques of treating venous disorders. We offer a six figure salary and bonus potential, along with malpractice insurance and health benefits. And since there are no weekend hours and a 40-hour work week, you will have plenty of leisure time. You won't have to worry about soliciting for patients or fighting insurance companies.

This is an outstanding opportunity for professional and financial advancement. If you are motivated to build a rewarding practice with the leader in the treatment of venous disorders, send your resume to:

Medical Director
Vein Clinics of America
2340 S. Arlington Heights Road
Arlington Heights, Illinois 60005

INTERNAL MEDICINE PHYSICIAN needed for family oriented south-central Washington community. Join medical staff of 20 physicians at very successful hospital. Must be BC/BE. Practice full range of Internal Medicine. First year income guarantee and other assistance. Excellent schools and recreation. Service area of 45,000. Contact Kimberley Rodkey, (509) 837-2101, ext 170.

FAMILY/GENERAL PRACTITIONER needed for beautiful agricultural south-central Washington community. Join medical staff of 20 physicians at very successful hospital. Must be BC/BE and do OB. Complete full practice assistance package offered. Service area of 45,000. Contact Kimberley Rodkey, (509) 837-2101, ext 170.

IDAHO. Opportunity for high quality of life, low cost of living in beautiful Idaho—sunbelt of the Pacific Northwest. Join Family Practice teams at one of six multi-site Community/Migrant Health Centers providing primary care to rural communities. Outstanding four-season recreation, malpractice insurance paid, generous continuing education, competitive salary and benefits, loan repayment potential, and opportunity to provide OB services. Send résumé to Dean Hungerford, Idaho Primary Care Association, PO Box 6756, Boise, ID 83707; or call (208) 345-2335.

(Continued on Page 125)

(Continued from Page 124)

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

SAN JOSE, CALIFORNIA. Pre-paid medical group (HMO) looking for dynamic BE/BC residency trained Family Physician. Extensive fringe benefits, including malpractice coverage. Immediately available opening. Send CV to James Conroy, MD, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119; or call (408) 972-6339.

WELL ESTABLISHED NORTHERN CALIFORNIA THREE-MAN GROUP seeks BE/BC Orthopaedist. Guaranteed first year salary with benefits. Metropolitan area of 250,000, 90 minutes to San Francisco. Practice—general Orthopaedics including Trauma, Arthroscopy, Reconstructive and Sports Medicine. Submit inquiries to Mary L. Greer, Office Manager, 1520 N. El Dorado St, Stockton, CA 95204.

PART-TIME EXPERIENCED EMERGENCY PHYSICIAN needed in moderate volume, low trauma Emergency Department. Good compensation. Possibility of full-time position. Send CV to Pedro Febres, MD, Number 132, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NAPA VALLEY, CALIFORNIA—KAISER PERMANENTE. Well-trained Family Practitioner needed to join a small clinic and provide high quality, personalized care to our patients. Busy office and hospital practice but regular hours. Contact Ernest Arras, MD, 3284 Jefferson, Napa, CA 94558; or call (707) 252-5819.

INTERNIST BE/BC to join growing practice in Tacoma, Washington. Practice is oriented to women's health issues. Women encouraged to apply. Send CV to PO Box 2122, Gig Harbor, WA 98335; (206) 858-8686 evenings.

NORTHERN CALIFORNIA. Family Practice opportunity with Community Health Center. Modesto location. Salary plus incentive program. Spanish fluency desirable. Contact Michael Sullivan, Executive Director, Merced Family Health Centers, Inc, PO Box 858, Merced, CA 95341; (209) 383-1848.

ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

GENERAL INTERNIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

GASTROENTEROLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

EASTERN WASHINGTON. Year round golf, sunshine, Columbia River recreation. Community of 115,000 needs Family Medicine, Oncology, OB/GYN, Pulmonology, Neurology, Thoracic Surgery, and Pediatrics. Variety of life-styles within minutes of hospital. River-front, ranching, agriculture, vineyards. Medical community adding new specialties. Practice support available. Excellent schools. Send CV or call The Friedrich Group, 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 842-5248.

PHYSICIANS WANTED

EXCELLENT OPPORTUNITY IN SOUTHERN CALIFORNIA
GENERAL SURGEON
EQUITY IN ONE YEAR

Prestigious Orange County based General Surgeon looking for motivated team-player who welcomes the opportunity of joining a rewarding, prosperous private practice with state-of-the-art technology.

Excellent suburban environment to raise a family, located in an area of rolling hills, snow-capped mountain views, and horse riding trails. Adjacent to the hospital, free from urban stress, superior schools, beautiful homes attractively priced, and active community involvement.

The position offers an excellent 6-figure opportunity, bonus potential, health benefits, and CME.

This is an outstanding opportunity for a Board certified/eligible General Surgeon who is interested in building a solid career in private medical practice. Please send curriculum vitae or contact:

DAR & Associates Physician Recruiters
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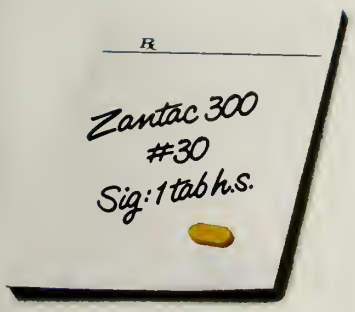

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Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

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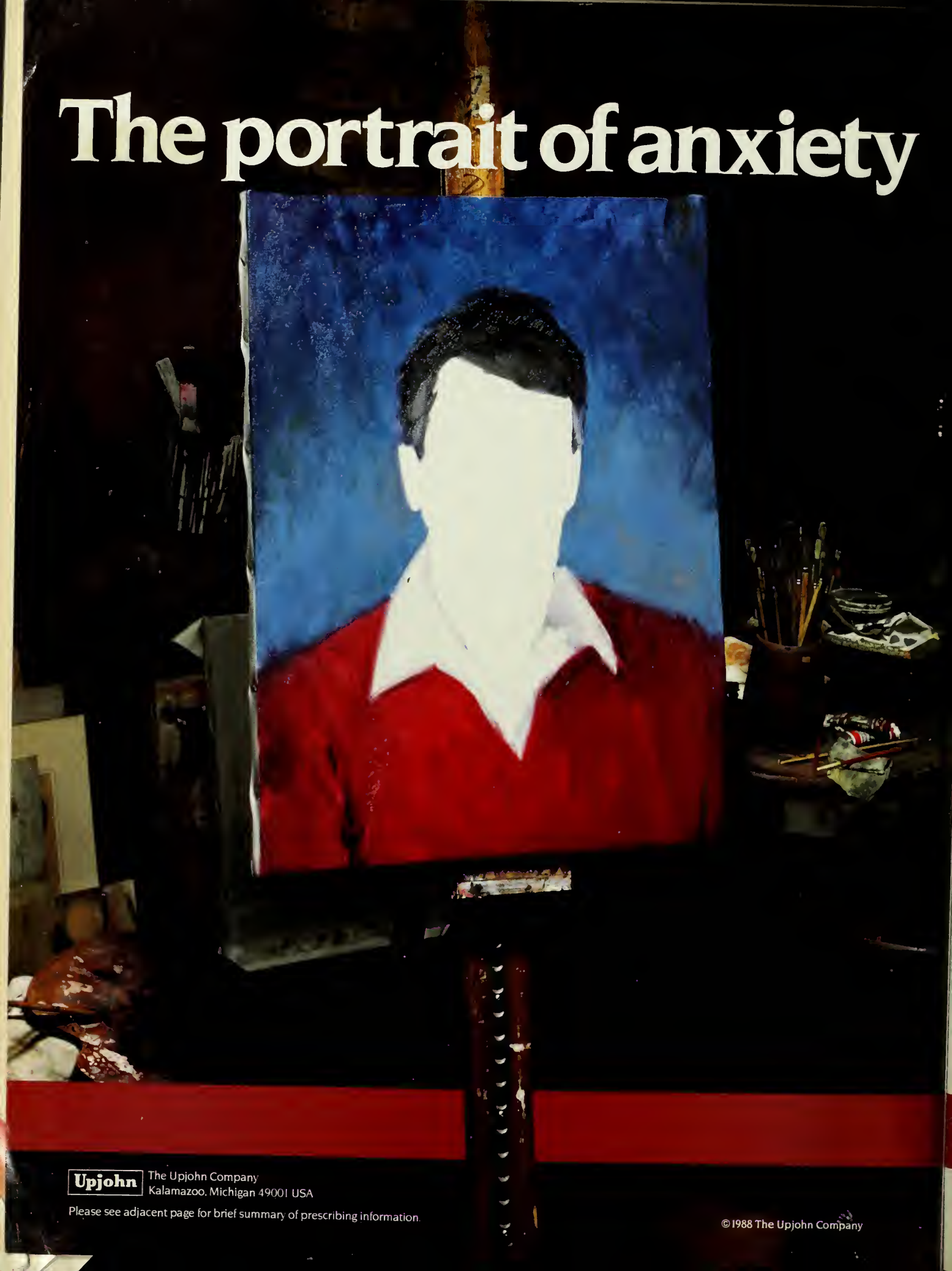
The portrait of anxiety



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Please see adjacent page for brief summary of prescribing information.

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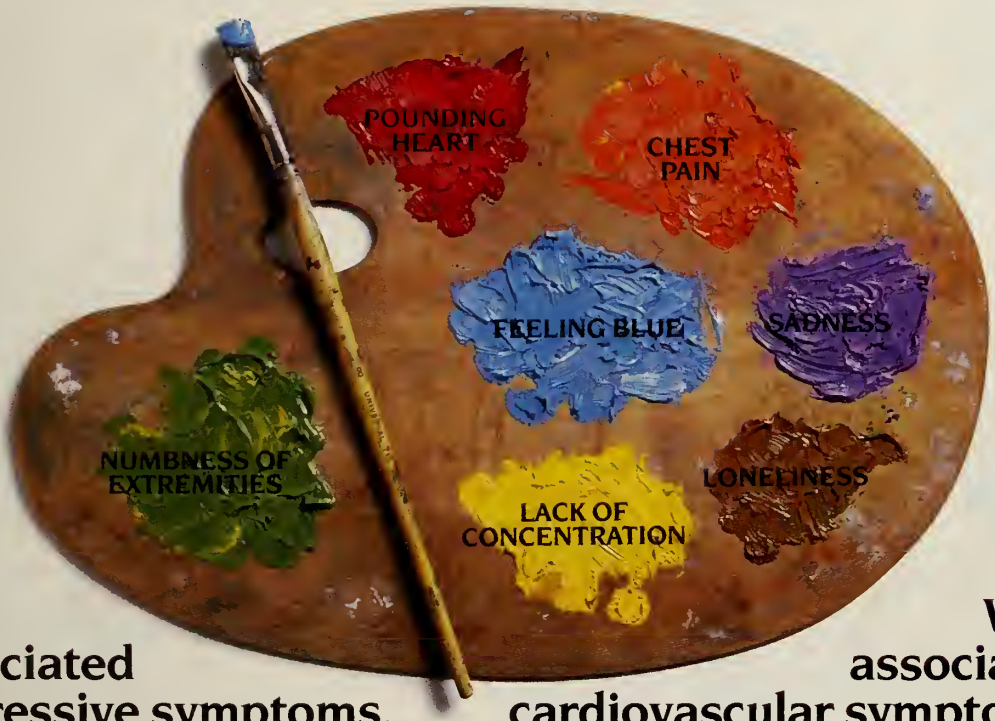
is often complicated



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In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

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- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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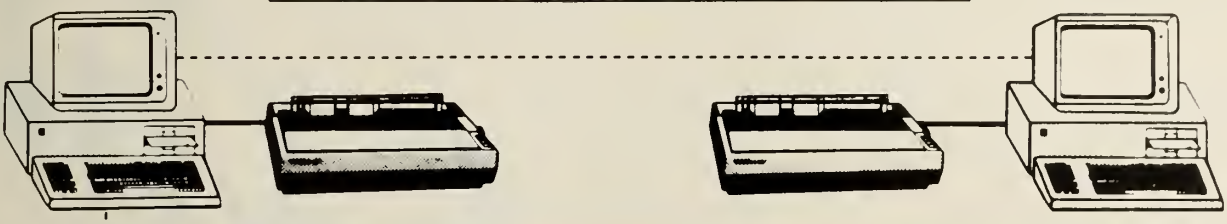

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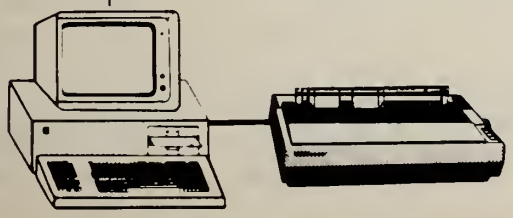

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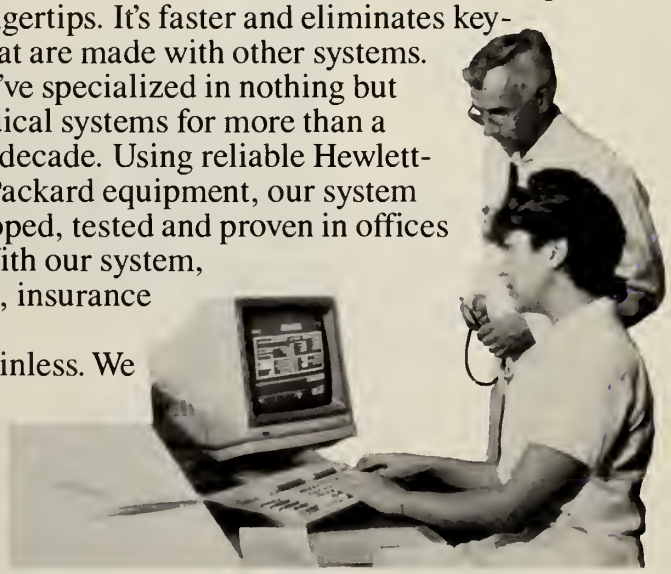

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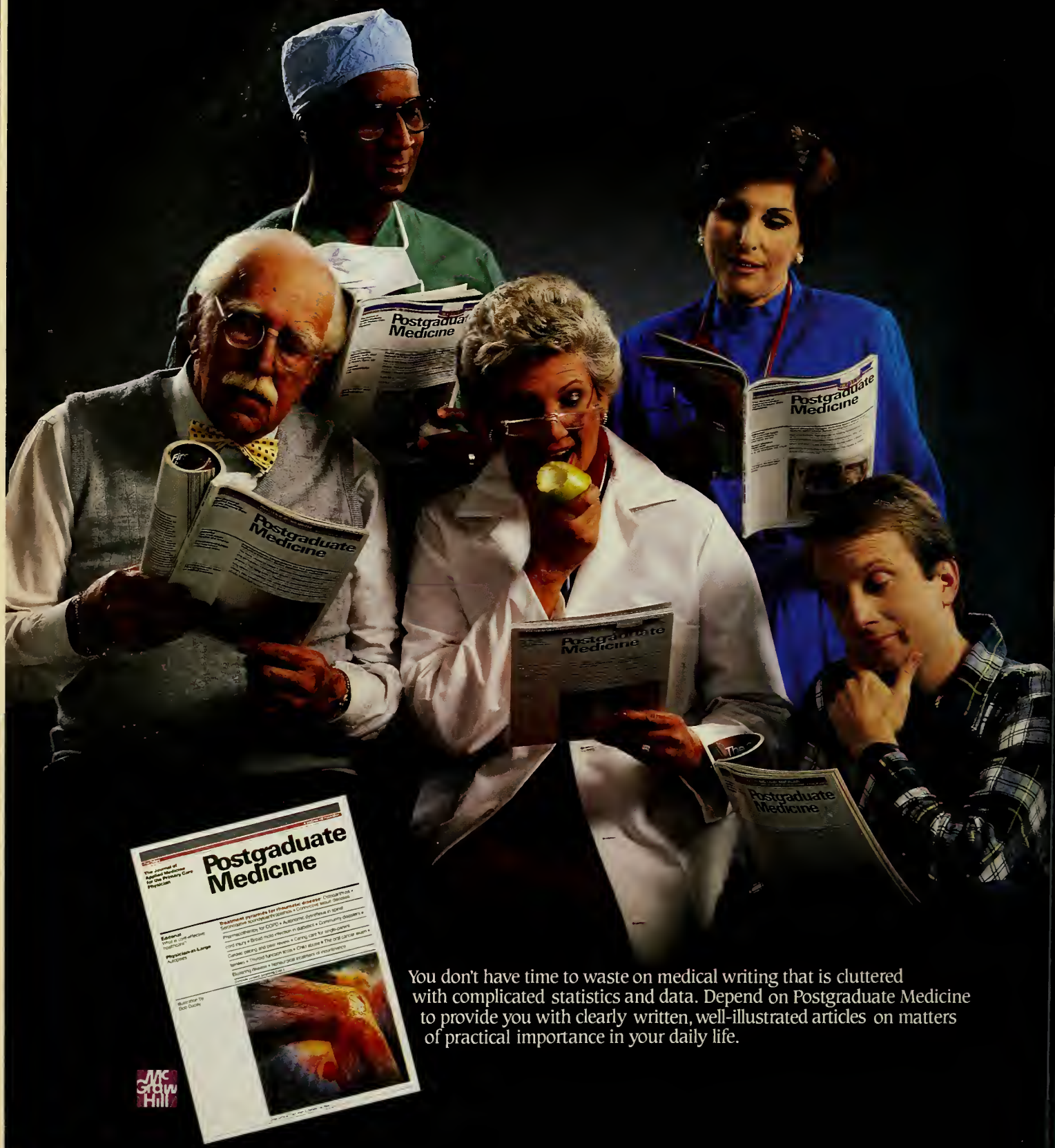

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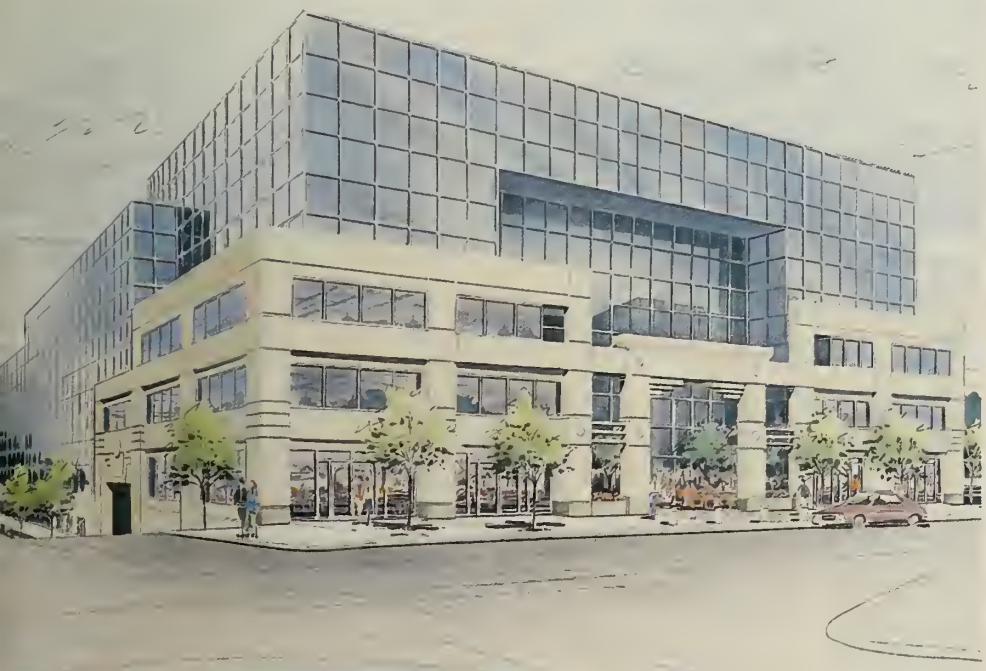

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Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

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1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987; 9(4):395-399.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 11—**Diabetes 1989: A Practical Approach to Management III.** Camelback Inn, Scottsdale. Sat. Contact: Helen Rentz, Good Samaritan Medical Center, (602) 239-5994 or 1-800-443-5972.

February 22-24—**12th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

February 24-25—**Case Studies in ECG Interpretation and Arrhythmia Management.** Clarion Inn at McCormick Ranch, Scottsdale. Fri-Sat. Contact: Medical Education Collaborative, (303) 989-9802.

February 24-26—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Shay Southwick, AzAFP, (602) 249-2021.

February 28-March 3—**Pediatric Update 1989.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Barbara Bengtson, Phoenix Children's Hospital, (602) 239-4350.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

March 9-11—**Current Management of Central Nervous System Tumors.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1-800-BARROW-1.

March 30-April 1—**25th Annual Arizona Chest Symposium.** Westin LaPaloma, Tucson. Thurs-Sat. Contact: Susan Thornton, Tucson Medical Center, (602) 327-5461, ext 5110.

April 3-4—**Mayo Clinic Scottsdale Clinical Reviews.** The Registry Resort, Scottsdale. Mon-Tues. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

April 28-29—**Recent Advances in Cardiovascular Diseases.** The Registry Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

February 27-March 2—**17th Obstetric Anesthesia Conference.** Dept of Anesthesiology Ohio State at Sheraton Waikiki Hotel, Hawaii. Mon-Thurs. Contact: Arlene Rogers, Ohio State University Hospitals, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 16-19—**Obstetrical Anesthesia: 1989.** UCSF at Hotel Meridien, San Francisco. Thurs-Sun. Contact: Anita Edgecombe, UCSF, C 450, Box 0648, San Francisco 94143-0648. (415) 476-2273.

March 18-19—**34th Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

February 15—**29th Annual Cardiology Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. Contact: Bonnie Wells, Enloe Hospital. (916) 891-7375.

February 24-25—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Grand Hotel, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 9-11—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at Maui, Hawaii. Thurs-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

March 10-11—**Risk Factors for Cardiovascular Disease: Lipids, Diabetes and Hypertension.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. $200. Contact: UCSF.

March 16-18—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Westin Maui Hotel. Thurs-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

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Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema. Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium. VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, it concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use. Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 298 patients.

Hypertension. The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure. The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (79%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category.

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest, pulmonary embolism and infarction; rhythm disturbances, atrial fibrillation; palpitation.

Digestive. Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric. Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostate hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin. Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other. Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema. Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes. Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen. In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J6VS18R(815)

MSD
MERCK SHARP & DOHME

Her anxiolytic is working—but she's alert, functioning, and at no risk of a benzodiazepine withdrawal syndrome when therapy ends.

BuSpar relieves anxiety and returns your patient to normal activity

...with no more sedation (10%) than induced by placebo (9%)[1]
...without inducing significant cognitive[2] or functional impairment*
...without producing a benzodiazepine withdrawal syndrome[3] upon discontinuation

Effective choice for anxiety

BuSpar®

Tablets, 5 mg and 10 mg

(buspirone HCl)

for a different kind of calm

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

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MJL8-4225R2

BuSpar® (buspirone HCl)

References: 1. Newton RE, *et al.* A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Luckin I, *et al.* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances, infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL 8-4225R2

Mead Johnson PHARMACEUTICALS

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CONTINUING MEDICAL EDUCATION

(Continued from Page 146)

March 31-April 1—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 14-15—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Las Vegas, Nevada. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

April 24-May 3—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn. 1½ weeks. 40 hours. $900. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Fisherman's Wharf. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 24—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

July 15—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 154)

YOU CAN REACH THE GREEN FASTER WITH SCPIE'S NEW AGE 55 RETIREMENT PLAN

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SCPIE is on top of the leader board. It's worth a call to find out what we can do for your retirement game.

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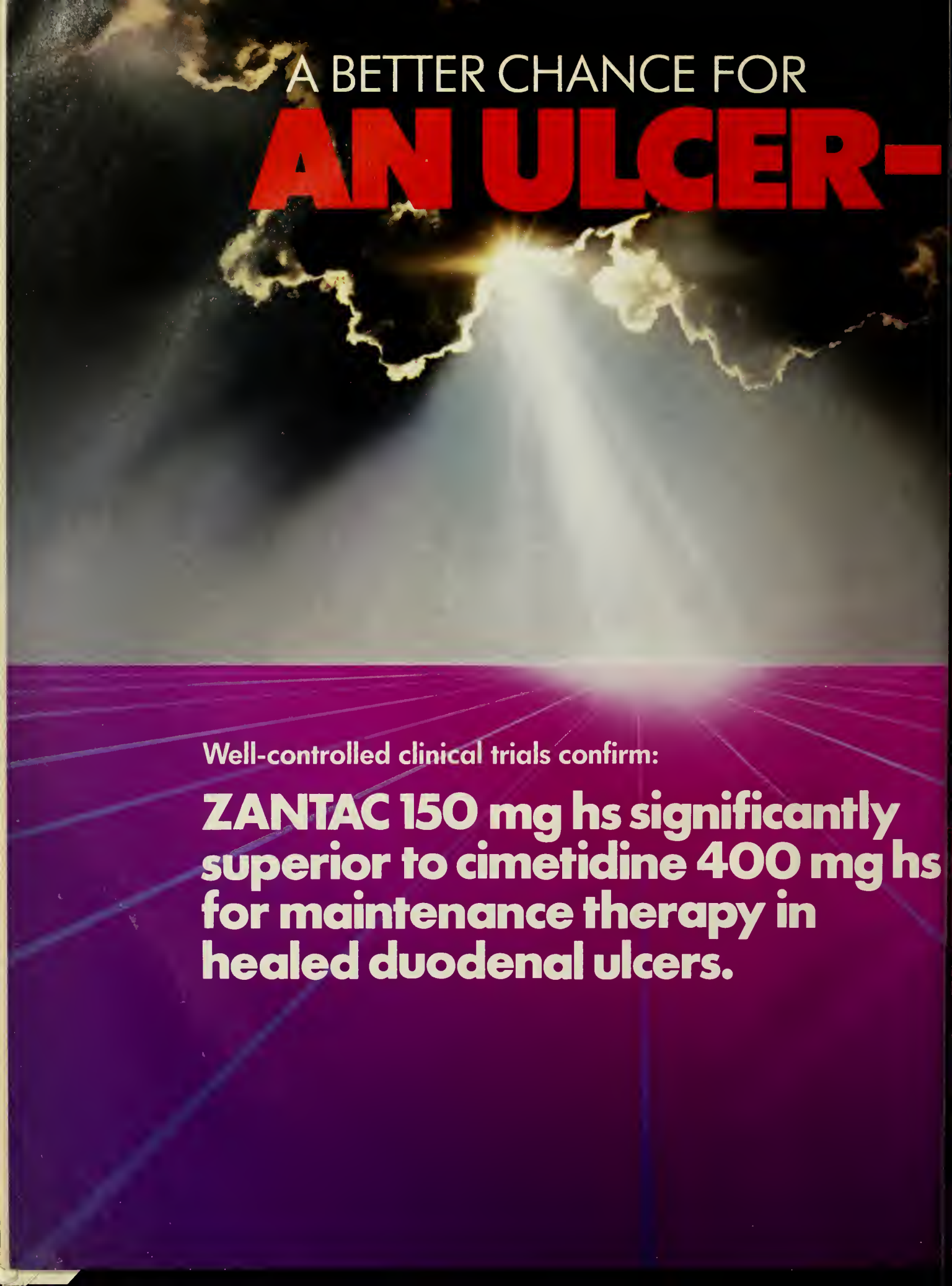
A BETTER CHANCE FOR
AN ULCER–
Well-controlled clinical trials confirm:
ZANTAC 150 mg hs significantly superior to cimetidine 400 mg hs for maintenance therapy in healed duodenal ulcers.

FREE FUTURE

Percent of patients ulcer-free after 1 year of therapy

ZANTAC 150 mg hs (n = 60)	84%*
cimetidine 400 mg hs (n = 66)	57%
ZANTAC 150 mg hs (n = 243)	77%†
cimetidine 400 mg hs (n = 241)	63%

*P = 0.01 †P = 0.0004 % life-table estimates

All patients were permitted prn antacids for relief of pain.
Adapted from Silvis[1] and Gough.[2]

These two trials[1,2] used the currently recommended dosing regimen of cimetidine (400 mg hs) and ranitidine (150 mg hs). A comparison of other dosing regimens has not been studied.
The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.
The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Glaxo/ ROCHE

See next page for references and Brief Summary of Product Information.

References. 1. Silvis SE, Gruttin J, Hardin R, et al. Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487. 2. Gough KR, Korman MG, Bardhan KD, et al. Ranitidine and cimetidine in prevention of duodenal ulcer relapse: A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984;2:659-662.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer; hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTINUING MEDICAL EDUCATION

(Continued from Page 150)

July 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: Deborah Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

June 2-3—**Southwestern Regional Cutaneous Flap Workshop.** UCLA Center for Health Sciences. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

June 25—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 16—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

March 2-5—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Sheraton Universal, Los Angeles. Thurs-Sun. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

April 5-7—**Advances in Emergency Medicine.** UCSF at Stanford Court, San Francisco. Wed-Fri. $380. Contact: UCSF.

April 26-28—**8th Annual Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Wed-Fri. 17 hrs. Contact: Orange County Trauma Society, 321 N Rampart, Ste 100, Orange 92668. (714) 937-5030.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 19-23—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 23-24—**Advanced Cardiac Life Support.** Center for Health Education at Long Beach. Fri-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 24-25—**11th Annual Poison Center Symposium: Emergency Medicine and Toxicology.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $280. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

January-June—**Seminars in Cytopathology 1989.** UCSF at Health Sciences Room 300. Thurs/monthly. 12 hrs. $140 full series/$30 single. Contact: UCSF.

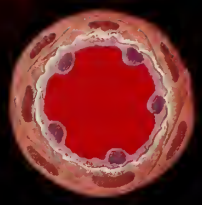
February 15-17—**22nd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15.5 hrs. $345. Contact: UCSF.

February 17-18—**Advances in Skin Cancer Management: A Multi-Specialty Approach.** UCSF at Ramada Renaissance Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

(Continued on Page 234)

THE INSIDE/OUTSIDE STORY
IN HYPERTENSION

Effective peripheral vasodilation[1]



Undiminished cardiac output[2]

Undiminished renal function[3-5]

Uncompromised vitality

- ☐ Low incidence of fatigue and impotence[6,7]
- ☐ Undiminished exercise capacity[8]
- ☐ High level of patient acceptance

Effective blood pressure control

TRANDATE® *bid*

labetalol HCl/100 mg tablets

Because it vasodilates

Please see references and Brief Summary of Prescribing Information on adjacent page.

Allen & Hanburys™
Division of Glaxo Inc., Research Triangle Park, NC 27709

References: 1. Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75:24-31. 2. Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. 3. Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75(suppl 4A):103-108. 4. Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. 5. Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S. 6. Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:285-293. 7. Due DL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 8. Feit A, Holtzman R, Cohen M, et al: Effect of labetalol on exercise tolerance and double product in mild to moderate essential hypertension. *Am J Med* 1985;78:937-941.

TRANDATE® Tablets **BRIEF SUMMARY**
(labetalol hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will

TRANDATE® (labetalol hydrochloride) Tablets

be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat; laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

April 1988

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CALIFORNIA MEDICAL ASSOCIATION

PRESENTS

118TH ANNUAL SESSION AND

Western Scientific Assembly

MARCH 3-8, 1989
DISNEYLAND HOTEL • ANAHEIM

WESTERN SCIENTIFIC ASSEMBLY

GOLDEN APPLE AWARD

Rene Cailliet, MD

Rene Cailliet, MD, Director of Rehabilitation Services at the Santa Monica Hospital Medical Center, has been selected by the Committee on Scientific Assemblies to receive CMA's 1989 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents. Doctor Cailliet held the post of Chairman, Department of Rehabilitation Medicine at USC from 1972-1982, and is currently professor emeritus of rehabilitation medicine; he is also the author of seven books on pain.

The award will be presented following Doctor Cailliet's presentation, "Conservative Management of Low Back Pain." All are invited to attend. Come hear an outstanding teacher address a subject of interest to all physicians.

Conservative Management of Low Back Pain
Friday, March 3, 12:30 pm
Disneyland Hotel

California Medical Association's 1989 Western Scientific Assembly will be held March 3-8 at the Disneyland Hotel. Persons attending scientific courses or special conferences are asked to register on site in the Center Lounge, located in the foyer outside the Grand Ballroom of the Disneyland Hotel. For more information on the following programs, please contact CMA at (415) 541-0900.

THURSDAY, MARCH 2

- ❑ Basic Cardiac Life Support

FRIDAY, MARCH 3

- ❑ Advanced Cardiac Life Support: Certification
- ❑ Clinical Applications of Environmental Epidemiology
- ❑ Managing HIV Infection
- ❑ Neurology Update for the Primary Care Physician
- ❑ Sports Medicine: Working With the Weekend Warrior
- ❑ Occupational Medicine Controversies
- ❑ New Perceptions in Treating Cerebral Palsy
- ❑ Pulmonary Medicine in Your Office
- ❑ Current Trends in Emergency Medicine and Prehospital Care
- ❑ Clinical Cardiology for the Primary Care Physician

SATURDAY, MARCH 4

- ❑ Advanced Cardiac Life Support: Recertification
- ❑ Fine Needle Aspiration Biopsy
- ❑ Lumbago 1989
- ❑ Controversies in Dermatology
- ❑ Women's Health Care Issues in Family Medicine
- ❑ Rheumatoid Arthritis
- ❑ Update in Ophthalmology
- ❑ Advances in Pediatrics
- ❑ A Workshop on Residency Selection and Career Planning
- ❑ Preoperative Fluid, Electrolyte and Blood Transfusion Management
- ❑ Multidisciplinary Approach to Biliary Stone Disease
- ❑ Physician Lifestyles: There's Gotta Be a Pony in Here Somewhere
- ❑ The Role of Modern Psychopharmacology
- ❑ Investment Planning

SUNDAY, MARCH 5

- ❑ Skin Cancer Update
- ❑ Colorectal Cancer Workshop - Flexible Sigmoidoscopy
- ❑ Pediatric Allergy - New Perspectives
- ❑ What's New? Keeping Up-To-Date in Obstetrics and Gynecology
- ❑ Update on Sexually Transmitted Diseases
- ❑ Update on the Tobacco Revolution
- ❑ Urology Update for the Primary Care Physician
- ❑ Legal Problems of Impaired Physicians
- ❑ Diagnosis and Management of Vertigo and Sleep Disorders
- ❑ Molehills or Mountains?
- ❑ Physicians and the Law
- ❑ CMA Takes a Look at the Washington Scene
- ❑ Magic Machines: Making Computers Work For You

MONDAY, MARCH 6

- ❑ Senior Health Care Seminar
- ❑ Suture Course
- ❑ Current Update on the Management of Breast Cancer

WESTERN SCIENTIFIC ASSEMBLY KEYNOTE SPEAKER

Willard Gaylin, MD

A noted ethicist, psychiatrist and psychoanalyst, Doctor Gaylin is co-founder and president of The Hastings Center in New York state,which is engaged in research on ethical issues in the life sciences. He is also a clinical professor of psychiatry at Columbia University's College of Physicians and Surgeons and author of many books, the latest of which is *The Rage Within: Anger in Modern Life.*

Many of the knotty legal, moral, and ethical problems associated with biomedical advances are special concerns of Doctor Gaylin. The Center's staff members and fellows are engaged in examining and evaluating issues involving population control, genetic screening, recombinant DNA research, behavior control, health policy, and the pros and cons of living wills.

The Burdens of Biomedical Success: After All We've Done for Them...
Sunday, March 5, 12:15 p.m. Disneyland Hotel

THE 118TH ANNUAL SESSION

AND WESTERN SCIENTIFIC ASSEMBLY

CONCURRENT EVENTS

HOUSE OF DELEGATES

The CMA House of Delegates meets Saturday, March 4 through Wednesday, March 8 at the Disneyland Hotel. Sit in on reference committee hearings and House sessions to see firsthand how CMA policies are shaped. Highlights of this year's House will be the farewell address of out-going CMA President Dr. Laurens P. White, a San Francisco internist, and the inaugural address of CMA's President-Elect, Dr. William G. Plested, a Los Angeles cardiovascular surgeon. Registration will be available March 3-8 at the Disneyland Hotel.

HOSPITAL MEDICAL STAFF SECTION ANNUAL ASSEMBLY

The CMA-HMSS Annual Assembly will be Friday, March 3 at the Disneyland Hotel. The theme of this year's assembly will be "Medical Staff Issues: 1989."

SPECIAL EVENTS

A variety of special events will be offered this year. Registration takes place at the Disneyland Hotel.

- ❑ Huntington Library, Art Gallery and Botanical Gardens
- ❑ Rags to Riches (Garment District to Beverly Hills)
- ❑ Newport Harbor Cruise/Dinner
- ❑ Gump's Presents Gems in General
- ❑ Laguna Impressions and High Tea at the Ritz Carlton
- ❑ Family Day at Disneyland

EXHIBITS

The exhibit hall offers something for everyone: pharmaceutical displays, computer and office systems, medical testing systems, insurance, investment opportunities, and much more. Prizes!

GENERAL INFORMATION

LOCATION

The CMA 1989 Western Scientific Assembly will be held at the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, CA 92802. Call (714) 778-6600 for hotel reservation information.

FEES

There is no charge to CMA members and their non-physician family members and guests for general registration, nor to registered nurses, residents, interns or medical students. A general registration fee of $300 is charged to non-member physicians. Nonmember fee can be applied towards first year CMA membership dues.

REGISTRATION

Advance registration closes February 10, 1989. Attendees may register on site at the Disneyland Hotel's Center Lounge. Registration will be open:

Thursday, March 2	**1:00 pm to 5:00 pm**
Friday, March 3	**7:30 am to 5:00 pm**
Saturday, March 4	**7:00 am to 5:00 pm**
Sunday, March 5	**7:30 am to 5:00 pm**
Monday, March 6	**7:30 am to 4:00 pm**

The registration desk will move to the House registration area outside the Marina Ballroom:

Tuesday, March 7	**9:00 am to 4:00 pm**
Wednesday, March 8	**9:00 am to 12:00 noon**

ANY QUESTIONS?

Contact CMA, (415) 541-0900.

Where do you go when you need to know more about your senior patients?

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Coming in the next issue:

- Alzheimer's disease: What do we know now?
- What to do for congestive heart failure
- Do senior patients need to stop smoking?
- How lab values for older patients vary from normal

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See complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product.*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) Injection by intravenous bolus.*

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses, for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

How Supplied: Tablets: *200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).*

Liquid: *300 mg./5 mL., in 8 fl. oz. (237 mL.) amber glass bottles and in single-dose units (300 mg./5 mL.), in packages of 10 (intended for institutional use only).*

Injection:

Vials: *300 mg./2 mL. in single-dose vials, in packages of 10 and 30, and in 8 mL. multiple-dose vials, in packages of 10 and 25.*

Prefilled Syringes: *300 mg./2 mL. in single-dose prefilled disposable syringes.*

Single-Dose Premixed Plastic Containers: *300 mg. in 50 mL. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

ADD-Vantage®* Vials: *300 mg./2 mL. in single-dose ADD-Vantage® Vials, in packages of 25.*

'Tagamet' HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Baxter Healthcare Corporation, Deerfield, IL 60015.

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BRS-TG-L7BB *Date of issuance Aug. 1988*

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Before prescribing, please see brief summary of prescribing information on adjacent page

Journal of the Arizona Medical Association

ARIZONA MEDICINE

FEBRUARY 1989, VOL. XLVI, NO.2

What Do Homeopathy, Naturopathy and Chiropractic Have In Common?

Marshall B. Block, M.D.

Although my father never got to college, he learned quickly that in his dental laboratory business his clients came first and in order to keep them interested he had to offer various options. He therefore set up several competing companies each offering the same product but each having a different payment plan. For instance, one company offered a "flat price" for a full denture (a "capitated system") while another company charged by the number of teeth the denture encompassed ("fee for service"). Each business had a different name and a different Post Office box number, but no matter which company received the work, the same technicians fabricated it. He smiled to himself when the same dentist sent work to several of his competing companies in order to save a few dollars. He felt he was giving his customers "options" and at the same time he was keeping his client base from eroding to competing operations which tried to offer lower prices and inferior quality work. I always thought that this was an ingenious scheme and one which many companies now utilize to their advantage.

It was thus "stimulating" to receive a phone call last week from a homeopathic physician berating me for telling a mutual patient that I did not believe in homeopathy. He asked, "Why couldn't I leave them alone and accept their presence in the medical community?" He furthermore stated that an endocrine peer cared for some of his patients and never disparaged his care. "Why did I?" On reflection, I came to the conclusion that I could not accept his therapy unless it was rigorously shown to be efficacious. I told him that my training did not permit me to accept unsubstantiated claims of diagnoses and therapy but that if he wanted to scientifically study his methods, I would offer him a format to publish his results in our state medical journal.

I then asked myself, "should these alternative forms of care be allowed to exist in order to give our population 'options' much like my father did for his customers? Was I wrong in suggesting that the scientific method should be the guidepost to use to assess medical diagnostic tests and medical therapy? Should we look the other way and not expect alternative methods to meet these standards? Has our society and thus our legislature required Boards of Homeopathy, Naturopathy and Chiropractic to meet the same standards that we set for medicine? In our age of technological advancement and cost consciousness, should not *all* therapies and diagnoses undergo careful and critical analysis and those found to be without merit dropped, whether they be advocated by medical physicians or others?"

At least my father was offering options which were of identical quality and worth. He only charged differently for the product. Here we have different products of uncertain worth being offered the same or higher prices. As physicians trained in the scientific method, we should not be ashamed to stand up and take a stand. Those who claim to help mankind as physicians should be able to prove their worth. As a first overture, I open these pages to them. We are biased in that we believe in the scientific method. It is a bias that we are proud of and we challenge them to emulate it.

Marshall B. Block, M.D.
Editor

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

FEBRUARY 1989, VOL. XLVI, NO.2

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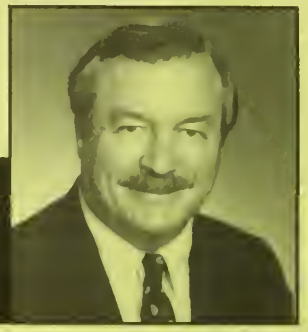
In This Issue::

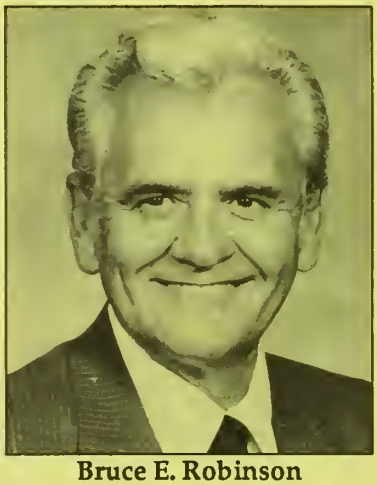
- Dean's Editorial
- Staff Profile
- Letter to the Editor
- New Members
- Classified

From Our President



Richard L. Collins, M.D.

To those of you who may not yet be aware, I want to take this opportunity to announce the unexpected death of our long-time Executive President, Bruce E. Robinson. This tragic event took place on the night of December 16-17, and saddened the holi-day season for many of us.



Bruce E. Robinson

Bruce would have reached his twenty-fifth anniversary of employment with the Arizona Medical Association in February of this year, an event which would have deserved recognition by all the physicians whom he has served over the years.

In spite of this tragedy, the Association's work is being carried out by a most capable staff who trained under Bruce. Chic Older, who has been an Assistant Executive Vice President, is serving as Acting Executive Vice President during this transition period. Meanwhile, a search for a person to assume the position permanently is underway. It is understood that Chic will be a candidate.

Bruce's death has been a shock to all who knew him, and it is our intent to dedicate the March issue of *Arizona Medicine* to him. At that time his life and his years with the Association will be reviewed by many who have known him well, but I couldn't let this issue of the journal go forth without an acknowledgment of Bruce's twenty-five years of dedication to the Arizona Medical Association.

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Pharmacologic Research

A morphine substitute that relieves severe pain without danger of respiratory depression or dependence; a drug to restore normal control of the urinary bladder in patients with incontinence; *in vitro* tests that accurately predict toxic effects of chemicals in humans. These goals are among the objectives of pharmacologic research at the College of Medicine and allied colleges, such as the College of Pharmacy and the Faculty of Science, as well as at the Barrow Neurological Institute and the Samaritan Rehabilitation Institute.

The Department of Pharmacology in the College of Medicine is the center of teams of basic and clinical pharmacologists, chemists and toxicologists that investigate mechanisms of drug actions at the molecular, cellular and whole-organism levels. Research in neuropharmacology, for example, is directed at the understanding of neural regulatory systems that may prove responsive to drug actions. A major recent accomplishment has been development at UA of peptide drugs that act selectively at delta opioid receptors in the brain and spinal cord to produce analgesia without many of them morphine-like side effects. The delta peptides differ from morphine because morphine acts primarily at mu opioid receptors. This exciting research grew from basic studies in the laboratory of multiple types of opioid receptors by a chemistry-pharmacology team that is unique in American universities. Pharmacologist members of the team are studying regulatory neuropeptide actions, not only in models of pain, but also for their gastrointestinal, cardiovascular and urinary bladder effects, with the goal of creating new ways to treat diarrhea and irritable bowel syndrome, hypertension, urinary incontinence and other disorders. Basic investigations of cellular receptors for many neurotransmitters and hormones provide new insight into regulatory mechanisms and new modalities of drug treatment.

Studies by biochemical pharmacologists and toxicologists reveal the mechanisms by which drugs, natural plant constituents and synthetic chemicals produce damage in liver, lung and kidneys. For example, the drugs or chemicals are often metabolized in the liver to highly reactive intermediates that interact with enzymes or genetic material in the liver, or are carried in the bloodstream to other organs to inflict damage. As knowledge concerning these mechanisms grows, it is becoming possible to predict from *in vitro* tests the potential toxicity of chemicals and avoid their use or produce analogues with less toxicity, thus improving the safety of drugs early in the development process.

Clinical pharmacologists, who are trained in medicine as well as research, study drug actions in the laboratory and in patients, thereby bridging basic and clinical science. Important aspects of ongoing clinical pharmacology research includes the mechanistic basis for optimal use of drug combinations and dosing schedules in the treatment of cancer, overcoming development of resistance to anticancer drugs, novel approaches to the management of diabetes, and characterization of new drugs for management of hypertension and cardiac arrhythmias.

Modern pharmacologic research utilizes an array of research techniques, from the molecular to the whole animal levels. For example, a research program in immunopharmacology directed at studies of mediators responsible for reactive airway disease has recently resulted in identification by molecular techniques of a new type of muscarinic cholinergic receptor in lung that may be responsive to selective blockade by drugs in the treatment of patients with asthma.

Continued on Page 10

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Join Us July 1-July 8

This is a first in a continuing series of introducing ArMA administrative staff to our member physicians. As time and space permit, it is our intent to show the "behind the scenes" aspect of association activities.

Janet Wendorff

One of my responsibilities working for both ArMA Financial Services and ArMA Membership Benefits include being the Office Manager. I work on the administrative end of a trust that ArMA sponsors. I open the accounts for Financial Services, along with making the necessary deposits. I am generally in a position to work with quite a few aspects of both subsidiaries. I have been with the Arizona Medical Association since July of 1987.

I have an Associate Degree in Science from Austin Community College, Austin, Minnesota. I was raised in Albert Lea, Minnesota, but because the job market in a town of that size is slim, I decided to move to St. Paul. I worked for a property management office and after 1 1/2 years, decided to expand my horizons and move to Arizona.

My parents will be arriving in the Valley for the month of February. The last relative I had who visited me was 1 1/2 years ago, and that was my sister who had the luck of catching Valley Fever. Needless to say, I am very excited for my parents' visit.

My hobbies include my cats, sports (both participating and watching), reading, and cooking. A great weekend includes spending time with friends, going out dancing and being fairly lazy on Sundays.

AMERICAN COLLEGE OF LEGAL MEDICINE

PRESENTS

The 1989 Annual Meeting of the College!

The Nuts and Bolts of Legal Medicine/Health Law Practice

March 1-4, 1989 at Marriott's Rancho Las Palmas Resort

Rancho Mirage, California

TOPICS:

Law and Forensic Medical Sciences; Direct & X-Exam of Medical Experts; Law & Pharmaceutical Industry; Staff and Board Disciplinary Action; Health Services & Law; Marketing Legal Medicine & Forensic Sciences; Effective Expert Testimony; Teaching Legal Medicine, etc.

Write to: Harold Hirsh, President, ACLM, M.D., J.D.,

P.O. Box 3190 Maple Glen, PA 19002

When I began my medical practice in Tolleson, Arizona over 25 years ago, if I would have performed an abortion, I would have lost my license to practice medicine. I would have been expelled from the medical society and been sent to prison.

In 1973 a supreme court justice, Harry Blackmun, who worked for nine years as resident counsel for the Mayo Clinic at Rochester, Minnesota, with one stroke of a pen, made it "all right" to do abortions, with no fear of losing my license to practice medicine, no fear of being expelled from the medical society, and no fear of going to prison.

I imagine Harry Blackmun came to trust the medical profession for its dedication to scientific analysis and the healing arts; and it is for this reason he said, and I restate it in layman's terms:

The medical doctor can be trusted to do what is right, if he abuses this trust, he'll get sued or the medical examiners will stop him. (paraphrased from 410 U.S. 166 *Roe v. Wade* (1973))

This same supreme court justice also admitted in *Roe v. Wade* that he did not know when life began (410 U.S. 159) but he knew that he could trust the medical profession to "do what is right."

Getting Away with Murder?

Letter to the Editor

Have we in a *"CONSPIRACY OF SILENCE"* breached the TRUST that this supreme court justice has placed in our hands?

Today if I prescribe the vitamin A analogue, isotretinoin, to a pregnant woman and her unborn baby in the first days of gestation, I very likely will see the teratogenic effects of isotretinoin in the baby, i.e. the fetal isotretinoin syndrome, and I will be calling my malpractice carrier to let them know what has happened.

You see, the minute I write a prescription for any pregnant woman, I am also writing it for her unborn baby, even if someone glibly tells me its just a "Glob of Tissue." I know, I now have more than one patient and all my treatment plans and prescriptions must acknowledge this. They are my responsibility!

Are we getting away with murder? I do not want to be implicated in an abuse of trust because, above all, it is wrong to do so, and also I fear that the victims of abortion may join in a class action lawsuit against the abortion/doctors who killed their babies.

The medical profession must break the *CONSPIRACY OF SILENCE* which perpetuates and condones the senseless killing of innocent preborn babies. (4000 everyday).

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Continued from page 4

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Seat Belt Law Reduces Mortality and Health Care Costs: Studies

The mandatory use of safety belts can significantly reduce motor vehicle accident injuries and deaths, as well as health care costs, conclude two studies in a recent *JAMA*.

A study of motor vehicle accident injuries in North Carolina before and after the state's mandatory seat-belt law was implemented provides strong evidence that the law has achieved its purpose in reducing injuries, saving lives and cutting health care costs, say the authors, Terence L. Chorba, M.D., M.P.H., of the Centers for Disease Control, Atlanta, and colleagues. They estimate that the North Carolina law may result in 1,100 fewer severe and fatal highway injuries per year.

The study examined crash data and injuries before the law went into effect, during a warning period, and after implementation of a fine for violators. It finds that a significant reduction in severe and fatal crash injuries among front-seat car occupants has occurred, especially since the fine went into effect. North Carolina's law became effective October 1, 1985, although until January 1, 1987, violators received only warnings. After that, front-seat occupants not wearing safety belts could be fined $25.

Studies such as this can help legislators and voters "determine whether mandating buckling up is worth the inconvenience and sacrifice of personal freedom" the authors say. "This study indicates that the North Carolina law has reasonably achieved its legislative intent," the authors conclude.

The accompanying study, by Elizabeth Mueller Orsay, M.D., of the University of Illinois, Chicago, and colleagues, indicates safety belt use can significantly reduce injuries and health care costs. The report is the first to use medical records rather than injury reports from police officers, the authors say.

The researchers studied 1,364 patients who were evaluated at four Chicago-area hospitals for traffic accident-related injuries. Of these, 791 (58 percent) had worn safety belts and 573 (42 percent) had not. Of the most severely injured, 81.8 percent had not worn belts at the time of injury. All five fatalities involved persons who were not protected, the authors report.

Only 6.8 percent of those who had worn belts required hospital admission vs 19.2 percent of those who had not used belts. The mean charges for patients who had not worn belts ($1,583) were nearly three times greater than those ($534) incurred by patients who had, they report. "Thus, safety belt wearers had a 60.1 percent reduction in severity of injury, a 64.6 percent decrease in hospital admissions, and a 66.3 decline in hospital charges," they conclude.

Auto accidents are the leading cause of death in Americans aged 5 to 34 and the seventh leading cause of death overall, Orsay and colleagues write. In 1982, an estimated 3.2 million people were injured in auto crashes, of whom approximately 1.4 million were treated in emergency departments and 350,000 required hospitalization. The overall economic loss to the United States attributable to these accidents in 1980 has been estimated at $57.2 billion. The Department of Transportation estimates that universal use of safety belts would reduce fatalities by 50 percent and injuries by 65 percent, the authors say.

More than 30 countries throughout the world have passed mandatory-use laws, the authors report. The United States is virtually the only developed nation that has not passed national safety belt legislation. To date, only 31 states and the District of Columbia have laws requiring safety belt use.

In an accompanying editorial, Diane Steed of the National Highway Traffic Safety Administration, Washington, D.C., says much more needs to be done to increase safety belt use in the United Sates, since more than half of America's motorists still drive unprotected. "I urge physicians and major health care providers, as part of their daily routine, to advise patients about the importance of safety belts and the use of child safety seats to prevent injuries from motor vehicle crashes," she writes.

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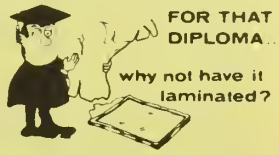

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Clinical Investigation

Screening Laboratory Tests for Crohn's Disease

DANIEL W. THOMAS, MD, *and* FRANK R. SINATRA, MD, *Los Angeles*

Presented in part at the Western Society for Pediatric Research, Carmel, California, February 3, 1987.

The prevalence of abnormal values of initial screening laboratory tests was assessed for 24 children who eventually proved to have Crohn's disease. The screening tests included in this analysis were fecal α_1-antitrypsin (FA) concentration, erythrocyte sedimentation rate (ESR), total leukocyte count, serum albumin level, hemoglobin concentration, and qualitative testing of stool for the presence of blood. Of the 24 patients, 21 had abnormal FA values, 17 had anemia, 19 had an increased ESR, 14 had hypoalbuminemia, rectal bleeding was found in 8, and none had leukocytosis. All 24 patients had at least one abnormal screening test value; the most frequently abnormal result was the FA concentration. Pediatric patients without elevated FA values, anemia, a high ESR, bloody stools, or hypoalbuminemia are unlikely to have active Crohn's disease.

(Thomas DW, Sinatra FR: Screening laboratory tests for Crohn's disease. West J Med 1989 Feb; 150:163-164)

The recognition of Crohn's disease can frequently be delayed because of its cryptic course and its varying clinical manifestations.[1] This is especially the case in children and adolescents in whom Crohn's disease can be confused with more common maladies, such as chronic recurrent abdominal pain or nonspecific diarrhea. This is a common clinical dilemma for primary care physicians. Although invasive diagnostic procedures and intestinal radiographs are usually necessary to confirm the diagnosis of Crohn's disease, screening laboratory tests are frequently done to select patients who warrant a more extensive evaluation.

The aim of this study was to establish the reliability of available noninvasive screening tests in pediatric patients who were eventually found to have Crohn's disease. We also endeavored to establish which of the available tests were most predictive of active disease.

Patients and Methods

Patients

We analyzed the records of 41 consecutive patients newly referred to the Gastroenterology Service at Childrens Hospital of Los Angeles who were subsequently found to have Crohn's disease.* Patients were sent to us by primary care physicians, other gastroenterologists, or were self-referred. Their symptoms were present for a mean of 15 months with a range of 2 months to 6 years. Of these patients, a complete set of initial laboratory test results was available for 24 who had active disease (subjective criteria[2]) but had not yet received therapy. Our analysis will focus on these 24 patients. In all, 17 patients were excluded from the study because the results of their screening laboratory tests were incomplete (6 patients), they already had a diagnosis of Crohn's disease and were receiving therapy (7 patients), or remission had been achieved following appropriate treatment (4 patients). There were 17 male patients; the age range was from 2.5 to 18 years with a mean age of 12.5 years. None of the patients were receiving therapy at the time of an initial laboratory assessment. All patients had typical radiographic, endoscopic, or histologic features of Crohn's disease.

This study was approved by the Committee on Clinical Investigations and Publications of Childrens Hospital of Los Angeles, September 8, 1978.

Laboratory Methods

The prevalence of abnormal screening test values was calculated for the following six clinical variables: elevated random values of fecal α_1-antitrypsin (FA; $\geq$ 3.4 mg per gram dry stool), anemia (hemoglobin $<$ 12 grams per dl), leukocytosis ($>$ 12,500 per μl), elevated erythrocyte sedimentation rate (ESR; $>$ 20 mm per hour), hypoalbuminemia (serum albumin $<$3.5 grams per dl), and rectal bleeding (gross or occult bleeding). Our laboratory has established that more than 99% of normal persons older than 1 year have FA concentrations of less than 3.4 mg per gram dry stool.[3] We determined FA levels on randomly collected stool specimens by a previously reported radial immunodiffusion method.[3] Fecal smears that were not grossly bloody were tested during the initial examination for the presence of occult blood with guaiac-impregnated filter paper (Hemoccult slides; Smith Kline Diagnostics, Inc, Sunnyvale, California).

Results

The prevalence of abnormal results of initial screening tests is shown in Table 1. Although none of the patients were noted to have leukocytosis, 8 of 24 showed a band cell count of more than 500 per μl. All eight children with bloody stools

*Russell Merritt, MD, and Philip Rosenthal, MD, participated in the care of these patients and provided helpful suggestions.

From the Division of Gastroenterology and Nutrition, Department of Pediatrics, Childrens Hospital of Los Angeles, and University of Southern California School of Medicine, Los Angeles.

Reprint requests to Daniel W. Thomas, MD, Division of Gastroenterology and Nutrition, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027.

ABBREVIATIONS USED IN TEXT

ESR = erythrocyte sedimentation rate
FA = fecal α_1-antitrypsin

had evidence of Crohn's colitis: seven had hematochezia and the other had occult bleeding. Elevated FA concentrations were found in 14 of the 16 without rectal bleeding, and 7 of 8 with rectal bleeding had abnormal FA concentrations. One patient had a borderline FA concentration of 3.2 mg per gram dry stool. The two other patients with normal FA concentrations later had elevated values at the start of therapy. At least one abnormal value on a screening test was found in each of the 24 patients, the most frequent (21/24) being that of fecal α_1-antitrypsin concentration; 22 of 24 had two or more abnormal results.

Discussion

Measuring the fecal α_1-antitrypsin excretion has proved to be a reliable assay for the presence of protein-losing enteropathy occurring in many gastrointestinal disorders.[2-13] Protein-losing enteropathy is one of the most common pathophysiologic abnormalities of the gut in patients with Crohn's disease. This has been shown in previous studies by chromated albumin Cr 51[14,15] and FA excretion[2,8] tests. There is a high degree of correlation between the presence of clinically active Crohn's disease and increased FA excretion.[2,8] Thus, it is not surprising that our results indicate that FA concentration was the most frequently abnormal initial screening laboratory test value that we found in children who later proved to have Crohn's disease. Determining the FA concentration appears to be particularly useful in recognizing the existence of an intestinal disturbance in patients without bloody stools. This may frequently occur in children with disease limited to the small intestine.

None of the children we studied had leukocytosis, but a significant proportion had an increase in immature neutrophils (band forms). Perhaps more thought should be given to including this latter criterion in objective scoring systems of Crohn's disease activity.

Our results suggest that pediatric patients without anemia, abnormal FA excretion, hypoalbuminemia, bloody stools, or an increased erythrocyte sedimentation rate are unlikely to have active Crohn's disease. Such findings in conjunction with the clinical evaluation are the impetus for proceeding with a more extensive assessment, regardless of the cause. These screening tests are not specific for Crohn's disease, however, and many other inflammatory disorders of the bowel can result in these abnormalities. The fecal α_1-antitrypsin level is frequently elevated in patients with infectious colitis as well as other conditions in which protein-losing enteropathy or intestinal bleeding is present (Table 2).[2-13] Our findings support a more widespread measuring of FA excretion as a screening test for intestinal disease.

TABLE 1.—*Prevalence of Abnormal Screening Test Values (n=24)*

Test	*Abnormal Values, No.*	*Range of Abnormal Values*
Fecal α_1-antitrypsin, mg/gram dry stool	21	4.2-20.4
Hemoglobin, grams/dl	17	8.1-11.9
Leukocyte count/μl	0	...
ESR, mm/h	19	30-120
Albumin, grams/dl	14	2.4-3.4
Rectal bleeding	8	...

ESR=erythrocyte sedimentation rate

TABLE 2.—*Disorders Known to Result in Elevated Fecal α_1-Antitrypsin Concentration*

Condition	*References*
Allergic enteropathy	3-5,7
Celiac disease	3,4,6,7
Chronic ulcerative colitis	3,5,6,8
Constrictive pericarditis,	5
cardiac failure	6
Crohn's disease	2,3,5,6,8
Gastrointestinal bleeding	3
Gastrointestinal infections	7,9,10
Graft-versus-host disease	11
Intestinal lymphoma	6
Intestinal lymphangiectasia	3,4,6,7
Hypertrophic gastritis	12
Necrotizing enterocolitis	13
Radiation enteritis	6

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Clinical Medicine

Compliance and Side Effects in Sleep Apnea Patients Treated With Nasal Continuous Positive Airway Pressure

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Nasal continuous positive airway pressure (CPAP) is an effective therapy for sleep apnea. We treated 144 patients with nasal CPAP and observed them for periods of as long as 25 months. No pneumothoraces occurred in any patient. Compliance rates were between 65% (90/139) and 83% (90/108), depending on the patient population considered. Demographic factors unrelated to discontinuing using CPAP included age, sex, and the presence of a housemate. Better-educated patients were less able to tolerate the equipment. Dry throat and nose and sore eyes were the most common side effects, but only sore eyes related to the amount of pressure. Side effects were unrelated to the number of months on the treatment, and obesity was related to higher pressures. Our study provides optimistic intermediate-term follow-up observations of patients on nasal CPAP therapy for sleep apnea. Whether adverse consequences occur over longer periods of time remains to be seen.

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Nasal continuous positive airway pressure (CPAP) therapy for sleep apnea was originally described in 1981[1] and is now a well-recognized, effective therapy for impaired respiration in sleep.[2-4] The long-term consequences of this intervention, however, and even the natural history of untreated sleep apnea, remain unclear. Until such data are available, the widespread use of CPAP by many thousands of patients requires a thorough evaluation of its compliance, side effects, and adverse reactions. Preliminary work on 24 cases suggests good compliance rates during the first year.[5] We report here on the intermediate-term efficacy and side effects in a larger group of patients followed up systematically.

Patients and Methods

We defined our sample as adult patients, 18 years or older, with diagnosed sleep apnea and originally treated with CPAP between July 1984 and June 1986 (N = 144). Patients were followed up by a questionnaire in August 1986 to allow a minimum of two months' experience for those (N = 90) who continued to use CPAP (Figure 1). Of the 144 patients, there were 3 deaths: brain-stem hemorrhage (a 68-year-old man), metastatic gastrointestinal carcinoma (a 52-year-old woman), and myocardial infarct (a 35-year-old morbidly obese man with a body mass index greater than 80). The first two patients used CPAP regularly. Two additional patients were excluded from follow-up analyses because they showed predominantly central apneas that did not respond initially in such a way as to justify the continued usage of CPAP. The demographics for the remaining 139 patients are shown in Table 1. A total of 42 of the patients had pulmonary disease. Of these, 37 suffered daytime dyspnea and 28 morning sputum production at least occasionally and 36 had a history of smoking in excess of 20 pack-years. Pulmonary function testing was not done routinely in our patients; however, 13 of the 42 patients routinely used theophylline or bronchial inhalers.

The patients who underwent our two-night CPAP protocol (to be described) represented an unselected, but certainly not random, subset of patients with sleep apnea seen in our clinic. We routinely presented CPAP as a treatment option to all patients judged to have clinically significant sleep apnea. Whether or not a patient then agreed to undergo the protocol—as did the 144 patients on whom this report is based—depended on many factors, including but not limited to third-party-payment issues; anxiety to the point of being unwilling to even attempt the protocol; a clear preference for surgical treatment to the point of being unwilling to even consider any other treatment option; and general recalcitrance. A comparison of our CPAP sample with all remaining adult patients undergoing an evaluation for sleep apnea during the aforementioned 24-month period is shown in Table 2. The CPAP group was significantly more obese and had more severe indices of sleep apnea than did the remaining clinic patients. To reiterate, the patients reported on here in no way represent a random sample of patients with sleep apnea, nor do they represent a random sample of sleep apnea patients seen in our clinic.

Most patients underwent a full night of baseline polysomnography in our sleep laboratory, although 20 polysomnograms were done elsewhere. Our CPAP protocol consists of two consecutive nights of polysomnography with pressure adjustments made on the first night and uninterrupted sleep with CPAP on the second. Conventional procedures for poly-

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
NS = not significant
RDI = respiratory disturbance index

somnography outlined elsewhere[6,7] were used on all nights, and Biox II or III ear oximeters were used. For convenience in sleep stage scoring,[7] we combined stages 1 and 2 and stages 3 and 4. We calculated desaturation indices of less than 90% and less than 80% by dividing the number of desaturation measurements by hours of sleep. In 28 patients, CPAP was started on the baseline night because of extreme severity of apnea. In these cases the baseline sleep measurements were calculated only for the first portion of the night. All sleep measurements during CPAP were based on the second night of CPAP of our two-night protocol. The pressure was delivered through the Respironics Nasal CPAP System (model SleepEasy).

The follow-up questionnaire is shown in Figure 2. Although any such survey instrument is limited by the veracity of self-reporting, a questionnaire does provide some cursory estimate of the frequency of side effects. Such estimates might also be a useful first step in examining the frequency of usage—for example, by more objective means[8]—or in designing clinical trials aimed at reducing the side effects of nasal CPAP. Our response rate on the mail questionnaire was relatively high (80.5%) because of telephone follow-up of the initial mailing. For those patients unwilling to complete the form, the reason for discontinuing CPAP was ascertained from a telephone interview for every case.

TABLE 1.—*Demographics of 139 Patients Using Continuous Positive Airway Pressure*

Sex	121 men, 18 women
Age, yr (range)	Mean 52.8, SD±12.4 (19-80)
Height, cm	Mean 176, SD±9.2
Weight, kg	Mean 117, SD±28.0
Body mass index	Mean 35.4, SD±8.4
Education	47.8% graduated high school or less 52.2% partial college education or higher
Housemate	13% lived alone

SD=standard deviation

Data were analyzed with parametric or nonparametric tests depending on the normality of distribution of the dependent variable. For normally distributed data, we used *t* tests for between-group comparisons and matched-pair *t* tests for within group comparisons. For non-normally distributed data, we used Mann-Whitney tests for between-group comparisons and Wilcoxon signed rank tests for within-group comparisons. We used χ^2 tests for comparing categoric data across groups. In the χ^2 tests, Yates' corrections were used when expected cell frequencies were less than 5.

Results

Pneumothorax did not develop in any of our patients. The polysomnographic data confirmed the efficacy of nasal CPAP in improving oxygenation substantially, reducing the number of disturbed breathing events, and restoring the sleep architecture to normal (Table 3). Despite this efficacy, only 90 patients continued to use CPAP when followed up in August 1986. Of the 49 persons giving up CPAP, 7 had undergone an unsuccessful upper airway operation in the past and elected not to resume the use of CPAP, 18 had no other current or past treatment, and 24 underwent other apparently successful treatments as of August 1986. These treatments included the following: an upper airway operation either successfully carried out in the past or in progress (15 patients); a tracheostomy done elsewhere after a trial with CPAP (4 patients); a tongue-retaining device prescribed elsewhere (2); gastric stapling associated with a significant weight loss (2); and low-flow oxygen (1). In some of these 24 patients, alternative treatments may have been chosen because of dissatisfaction with nasal CPAP.

Several different estimates of compliance can be derived from these figures. For example, if we assumed the patients choosing other treatments did so primarily because of dissatisfaction with CPAP, we obtained a somewhat strict compliance estimate of 64.7% (90/139). A more liberal compliance estimate (83.3%) related only those patients able to tolerate CPAP to those who chose no other treatment (90/108). An intermediate estimate of compliance (78.3%) included the 18 patients who did not use CPAP and the 7 who had an unsuccessful operation and did not resume using CPAP (90/115). For purposes of further analysis, we used the latter 25 cases as a comparative CPAP-discontinued group.

The primary reasons for discontinuing treatment in the

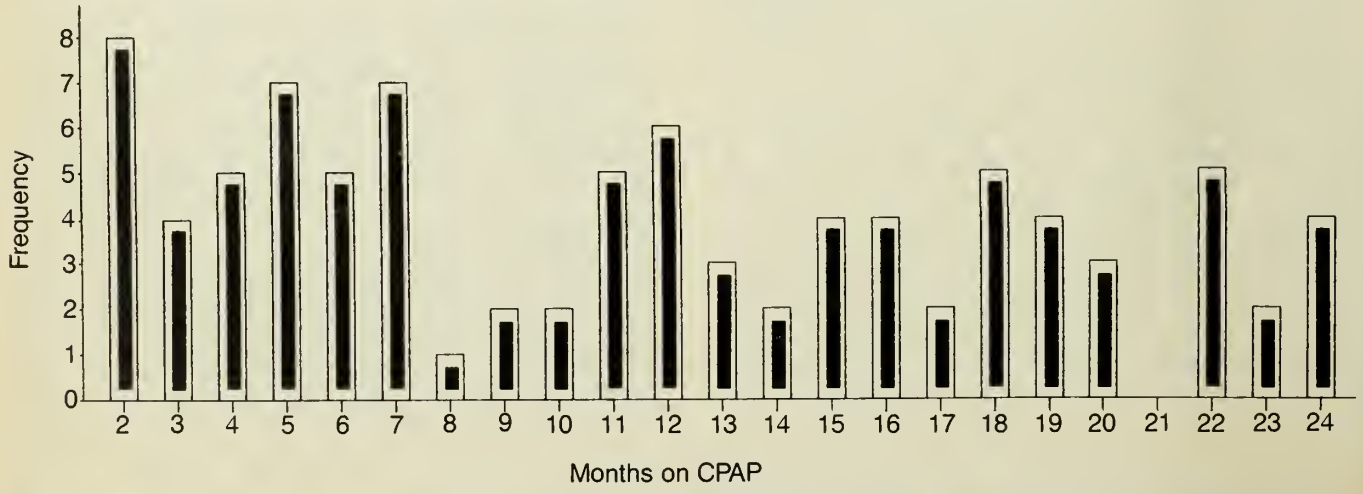

Figure 1.—The frequency histogram shows the number of months on nasal continuous positive airway pressure (CPAP) therapy for 90 patients with at least two months of use (current CPAP group).

TABLE 2.—*Patients Using Continuous Positive Airway Pressure (CPAP) and Remaining Patients Undergoing Sleep Apnea Evaluation*

Descriptor	Evaluation: CPAP Patients, N=139 Mean±SD	Evaluation: Other Patients, N=523 Mean±SD	Significant Difference
Male, %	87.1	80.9	NS
Age, yr	52.8±12.4	50.5±12.9	NS
Body mass index	35.4± 8.4	30.5± 7.2	t= 7.28, P<.0001
Respiratory disturbance index	80.8±38.8	37.1±36.0	t=11.78, P<.0001
Lowest SaO_2 % REM sleep	63.6±17.8	79.9±14.4	t=10.19, P<.0001
Lowest SaO_2 % non-REM sleep	72.3±14.2	83.3±11.0	t= 9.24, P<.0001
SaO_2<90% index	62.4±53.2	18.3±34.2	t=11.14, P<.0001
SaO_2<80% index	24.4±43.2	6.1±19.8	t= 6.85, P<.0001

NS=not significant, REM=rapid eye movement, SaO_2=arterial oxygen saturation, SD=standard deviation

comparative group were physical side effects (7 patients), dislike of the system (5 patients), and insomnia or anxiety (5 patients). The other eight patients discontinued using CPAP for miscellaneous reasons. The physical side effects included tinnitus, otitis media, dry mouth, and mask-induced facial pain. Of the 25 comparative cases, 10 used CPAP at home for two weeks or less, though one person used it for 17 months (mean, 3.6 months). Those patients who discontinued using CPAP within two weeks did so because of anxiety or dislike of the system.

The group currently using CPAP and the CPAP-discontinued group are compared in Table 4. Except for educational level, no other demographic feature distinguished the groups. In addition, no differences were seen between the groups in the proportion suffering from pulmonary disease. The CPAP-discontinued group had relatively less severe sleep apnea on baseline polysomnography but still showed substantial sleep-disordered breathing and oxygen desaturation, and it also showed less improvement in sleep oxygenation measures than the current CPAP group.

The mean weight for the group currently using CPAP was 117 kg at baseline and 110 kg at follow-up (t=4.38, P < .001). Although this was a statistically significant decrease, pronounced weight loss was infrequent. Only 17 patients lost more than 10% of their baseline weight, and only 5 lost more than 20% of their baseline weight. There was no relationship between months on CPAP treatment and weight loss (r = −.09, not significant [NS]).

The continuous positive airway pressure was delivered at pressures between 7.5 and 15.0 cm of water. The amount of pressure was unrelated to age but was correlated with body mass index at baseline (ρ = .32, P < .001) as well as with severity of sleep apnea on baseline (ρ = .32 with the respiratory disturbance index; ρ = .37, with < 90% O_2 index; ρ = .38 with < 80% O_2 index; all P < .001).

We examined by checklist the side effects experienced by the 90 patients regularly using CPAP at follow-up (Table 5) and the reasons for not using CPAP nightly (Table 6). None of the factors in Tables 5 and 6 were related to sex or having a housemate. A dry nose was more frequently reported by the older patients (r = .24, P < .05), but age was generally unrelated to side effects. The amount of pressure was also unre-

TABLE 3.—*Baseline and Continuous Positive Airway Pressure (CPAP) Sleep Data*

Sleep Variable	Baseline Mean±SD	CPAP Mean±SD	Significant Difference*
RDI†	80.8±38.8	9.9±14.3	z= 9.3
Stages 1 and 2, %	88.0± 9.2	70.8±14.6	z= 8.5
Stages 3 and 4, %	2.3± 6.7	9.6±10.5	z= 7.6
REM, %	8.2± 6.1	19.6± 9.4	t=10.6
Lowest SaO_2 % REM sleep	63.6±17.8	87.3±10.6	z= 8.4
Lowest SaO_2 % non-REM sleep	72.3±14.2	88.9± 5.6	z= 9.2
SaO_2 <90% index‡	62.4±53.2	2.5± 7.2	z= 9.1
SaO_2 <80% index‡	24.4±43.2	0.1± 0.6	z= 7.8

REM=rapid eye movement, SaO_2=arterial oxygen saturation, SD=standard deviation

*All differences significant at P<.0001.
†Respiratory disturbance index (number of episodes of apnea and hypopnea per sleep hour).
‡Desaturation index (number of desaturations per sleep hour).

1. If you are *not* using the CPAP device on a regular basis, please state reasons for discontinuing the treatment _____
_____.

   If you *are* currently using the CPAP device on a regular basis, please *continue* to answer this form.
2. Since you began to use the CPAP device, what percentage (%) of nights have you *not* used it? __%. (Although we do not expect an absolutely exact figure, try to be as accurate as possible.)
3. After using the device for a night, do you experience any of the following (circle whichever applies):
   (a) confusion and disorientation after waking
   (b) unusual sleepiness
   (c) unusual fatigue
   (d) headaches
   (e) dryness of the throat
   (f) dryness of the nose
   (g) buzzing in the ears
   (h) sore eyes
   (i) other; please explain _____
4. On the days when you have not used the device, the reason has been (circle whichever applies):
   (a) severe nasal obstruction caused by allergies or colds
   (b) unavailable electrical outlet
   (c) traveling without the device
   (d) failure of mask
   (e) failure of the device or other elements used apart from mask
   (f) being frightened of the device
   (g) being tired of using the device every night
   (h) disturbs sleep of bed partner
   (i) other; please explain _____

Rate satisfaction with CPAP from 1 to 10

1 2 3 4 5 6 7 8 9 10

(1 = very unhappy; 10 = very satisfied)

Figure 2.—This questionnaire was sent to patients using continuous positive airway pressure (CPAP) for sleep apnea.

TABLE 4.—*Groups Currently Using and Discontinued Using Continuous Positive Airway Pressure (CPAP)*

Patient Data	CPAP Use: Currently	CPAP Use: Discontinued	Significant Difference
Age, yr*	52.3±12.5	55.1±12.4	NS
Sex	12 F, 78 M	2 F, 23 M	NS
Body mass index*	37.2± 8.9	32.6± 6.2	t=2.94, P<.01
CPAP pressure, cm water*	12.5± 2.4	11.4± 2.6	z=1.77, P<.08
High school graduate or less, %	55.7	33.3	χ^2=3.77, P<.05
Has housemate, %	87.5	83.3	NS
RDI baseline*	84.8±43.5	69.9±28.9	t=1.95, P<.06
SaO_2<90% index baseline*	71.1±59.1	36.0±34.0	z=2.85, P<.005
SaO_2<80% index baseline*	31.9±50.1	7.0±15.2	z=3.05, P<.003
RDI change on CPAP*†	12.1±12.2	8.8±11.1	NS
SaO_2<90% index change on CPAP, mean†	−67.1	−37.1	z=2.44, P<.02
SaO_2<80% index change on CPAP, mean†	−32.9	− 6.4	z=2.79, P<.01

NS=not significant, RDI=respiratory disturbance index, SaO_2=arterial oxygen saturation

*Numbers are given as the mean ± standard deviation.
†Change score calculated as (post-CPAP value minus pre-CPAP value).

TABLE 5.—*Incidence of Side Effects From Continuous Positive Airway Pressure*

Side Effect	Incidence, %
Dry throat	69
Dry nose	52
Sore eyes	30
Headache	16
Unusual sleepiness	15
Unusual fatigue	15
Tinnitus	12
Other nasal problems including rhinorrhea	14*
Mask discomfort	6*

*Items were not included on checklist but were spontaneously reported.

TABLE 6.—*Incidence of Reasons for Not Using Continuous Positive Airway Pressure Nightly*

Reason	Incidence, %
Nasal obstruction	34
Travel	28
Tired of device	23
Mask failure	20
Inconvenient electrical outlet	12
Device failure	12
Partner disturbed	7
Afraid of device	2

lated to side effects, as were months on treatment, except that the amount of pressure was correlated with the symptom of sore eyes ($\rho = .27$, $P < .02$). Patients were generally satisfied with CPAP, giving a mean rating of 7.5 on a 1-to-10 scale. Satisfaction with CPAP was highest in those patients losing the most weight ($\rho = -.28$, $P < .02$). Nonetheless, only 60 patients reported using CPAP every night or nearly every night (95% or more of the time); far more likely was usage on at least a half-time basis (86 patients). Satisfaction was highly related to the percentage of nights when CPAP was used ($r = .43$, $P < .001$).

On baseline, patients with pulmonary disease did not differ from those without pulmonary disease in their respiratory disturbance index (86.3 versus 77.8, $z = .11$, NS), <90% O_2 index (69.0 versus 58.5, $z = 1.00$, NS) or <80% O_2 index (32.8 versus 20.3, $z = .33$, NS). On CPAP, pulmonary disease patients benefited equally well in terms of disturbed breathing events (for the respiratory disturbance index, 13.0 versus 9.1, $z = 1.14$, NS) though they still showed some mild desaturation (for <90% O_2 index, 4.7 versus 2.0, $z = 2.10$, $P < .05$; for <80% O_2 index, 0.3 versus 0.1, $z = 2.73$, $P < .01$). The pulmonary disease patients did not require higher CPAP pressures (12.7 versus 12.0, $t = 1.52$, NS), nor did they report more side effects than patients without pulmonary disease.

Discussion

Nasal CPAP appears to be well suited to most subgroups of patients studied here. Although the percentage of women in our study at 15% is greater than that reported in many studies, there was no suggestion that women had any more difficulty with nasal CPAP. This may be noteworthy in that, at least in some studies, women may be more prone to external disruption of sleep than men.[9,10] Of our 90 patients continuing to use CPAP, 15 were older than 65 years, suggesting that aged patients also were well suited for this treatment despite the fact that their sleep is physiologically more likely to be fragmented.[11] With growing concern over sleep apnea in the elderly and its possible consequences,[12,13] more geriatric patients may be using CPAP in the future. Finally, CPAP was effective in patients with pulmonary disease. No evidence of barotrauma has occurred in any of these latter patients, and the mean continuous positive airway pressure was similar.

When considering compliance, estimates should take into account all treatment options when patients discontinue nasal CPAP. In the strictest estimate of compliance (64.7%), those persons using CPAP as a temporary measure while awaiting an upper airway operation were considered noncompliant because such patients, having tried nasal CPAP and finding it effective, still opted for surgical treatment. Such an estimate may be biased against nasal CPAP, however, inasmuch as many patients simply prefer a surgical procedure over the nightly use of bedside equipment on an a priori basis. Obviously, any figures for CPAP compliance must take into account local treatment options available for patients with sleep apnea. Indeed, we think the availability of surgical treatment in our area makes this a more feasible choice than may be the

case elsewhere. Our compliance rates must also take into account our procedures for indoctrinating patients into nasal CPAP. In brief, we specially schedule each patient for an approximately one-hour daytime session with a polysomnographic technologist before the two-night CPAP protocol. This session, together with a weekly phone call from the technologist to the patient, particularly in the first few weeks of CPAP therapy, may promote compliance.

Why some patients discontinued using nasal CPAP and others did not was unclear. The group differences in change in oxygenation (Table 4) imply that those who discontinued may have received less symptomatic relief. As for other factors, none of the obvious demographics (age, sex, presence of a housemate) distinguished the patients who discontinued using nasal CPAP from those who did not. Curiously, the compliant group has had less formal education than the noncompliant group. The meaning of this finding is unclear. We speculate that the psychosocial impact of a mandatory nightly medical appliance is more tolerable to people who may be less skeptical of medical treatment in general. As an additional note, we must point out that even among our compliant group, nightly use was reported in only two thirds of the sample. As Krieger and Kurtz have suggested,[8] the veracity of such self-reported use may be discrepant from measurements of use based on actually using the CPAP unit. Nonetheless, it is clear that many patients apparently titrate their use without supervision by their physician. Whether such titration will ultimately have deleterious effects is unclear. What is clear is that any long-term follow-up study of CPAP patients must evaluate morbidity and mortality relative to the frequency of use.

Many of the physical side effects experienced by patients undergoing nasal CPAP may be ameliorated. For example, dryness of the upper airway and rhinorrhea are often improved with ultrasonic humidification, and soreness of the eyes suggests that an improperly fitting or worn mask should be replaced. We were impressed with the fact that the presence of such side effects was unrelated to the number of months on CPAP therapy. This suggests that the dry nose experienced by many CPAP patients, for example, does not lessen with the passage of time, but neither does it become worse. This is reassuring for those patients with few problems at the initiation of treatment. A simple dislike of the system and insomnia or anxiety played a major role in all of the patients giving up nasal CPAP rapidly. Nearly half of those patients giving up using nasal CPAP and opting for no other treatment did so in the initial two weeks. Apparently this initial period is the most critical and sensitive phase for adjusting to nasal CPAP and the time during which maximum support from the sleep clinic staff is required. Whether or not more frequent, such as daily, contact with staff would further increase compliance remains unanswered.

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Severe Thrombocytopenia in Epstein-Barr Virus-Induced Mononucleosis

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Severe thrombocytopenia is a rare complication of Epstein-Barr virus-induced infectious mononucleosis. We evaluated the clinical and laboratory data from seven patients seen between 1976 and 1985 whose lowest platelet counts varied from 3 to 25 × 10^9 per liter. Five of the seven patients were initially thought to have either acute leukemia or idiopathic thrombocytopenic purpura; eventually, however, primary Epstein-Barr virus infections were confirmed in all patients. Two of six patients tested had antiplatelet antibodies during the acute phase of their illnesses. Eight additional patients with acute disease who had only mild thrombocytopenia (94 to 144 × 10^9 per liter) were also tested for platelet antibodies with negative results. Steroid therapy was administered to three patients and platelet transfusions to one. All seven patients rapidly recovered with no serious hemorrhagic sequelae.

(Steeper TA, Horwitz CA, Moore SB, et al: Severe thrombocytopenia in Epstein-Barr virus-induced mononucleosis. West J Med 1989 Feb; 150:170-173)

While mild to moderate decreases in platelet counts—63 to 139 × 10^9 per liter—occur in approximately 50% of patients with Epstein-Barr virus (EBV)-induced infectious mononucleosis, severe thrombocytopenia is rarely seen in these patients.[1] In the present study, we describe seven patients with primary EBV infections whose lowest platelet counts varied from 3 to 25 × 10^9 per liter. In five cases, the clinical presentation was dominated by petechiae, ecchymoses, or bruising, and the initial diagnosis was either idiopathic thrombocytopenic purpura or acute leukemia. An effort was made to identify platelet autoantibodies in thawed specimens of serum taken during the acute phase of illness from six of these patients as well as eight other patients with infectious mononucleosis with only mild to moderate thrombocytopenia.

Patients and Methods

The cases of seven selected patients with EBV infectious mononucleosis whose lowest platelet counts varied from 3 to 25 × 10^9 per liter during the acute phase of illness were identified between 1976 and 1985 from the files of an ongoing EBV study by one of us (C.A.H.). These cases represented 0.9% (7/760) of cases of EBV infectious mononucleosis encountered during this interval. The diagnosis was made by findings on blood smears that met morphologic criteria described below in all cases (7/7) and either positive infectious mononucleosis-type heterophil antibody responses (5/7 cases) or serologically confirmed primary EBV infections (6/6 cases tested). Some of the details from two cases were included in earlier reports.[2,3] Eight other cases with lowest platelet counts between 94 and 144 × 10^9 per liter were also identified from 70 cases of heterophil-positive EBV-induced mononucleosis from 1986.

The minimal morphologic criteria for infectious mononucleosis include 50% mononuclear cells, 10 atypical lymphocytes per 100 leukocytes, and considerable heterogeneity among the lymphoid cells. Heterophil antibody studies were done by standard methods using a 2% suspension of horse erythrocytes following differential serum absorption with guinea pig kidney (GPK) or beef erythrocyte suspensions.[4] The results were interpreted as positive if the GPK-absorbed serum titer was greater than the simultaneously done beef cell-absorbed titer. They were recorded as negative if the GPK-absorbed serum titer equaled or was lower than the beef cell-absorbed titer.

Epstein-Barr Virus-Related Serologic Tests

Antibodies to viral capsid antigens (VCA) and the D (diffuse) and R (restricted) components of the EBV-induced early antigen complex were titrated by indirect immunofluorescence.[5,6] Antibodies to the EBV-associated nuclear antigen (EBNA) were determined by anticomplement immuno-

†Deceased

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ABBREVIATIONS USED IN TEXT

EBNA = Epstein-Barr [virus-associated] nuclear antigen
EBV = Epstein-Barr virus
GPK = guinea pig kidney
Ig = immunoglobulin
VCA = viral capsid antigens

fluorescence by techniques that have been described previously.[7,8] Serologic evidence of current or recent primary EBV infection in initial serum specimens was provided by the following criteria: the presence of VCA-specific immunoglobulin (Ig) M antibodies, high titers of VCA-specific IgG antibodies (≥1:320), the detection of anti-D (≥1:10), and the absence of anti-EBNA (<1:2). The results were confirmed when subsequent serum specimens showed a decline or disappearance of VCA-specific IgM antibodies and of anti-D and the emergence of anti-EBNA.[9] A past EBV infection was identified by constant VCA-specific IgG and EBNA antibody titers in serum specimens taken during the acute and convalescent phases. Most of these titers ranged between 1:40 and 1:160 and were not accompanied by IgM antibodies to VCA nor, as a rule, by anti-D. Low titers of anti-R are often noted in late convalescence from infectious mononucleosis and among healthy blood donors who constantly maintain relatively high levels of VCA-specific IgG. The absence of all EBV-related antibodies excludes past and recent EBV infections.

Tests for Platelet Antibodies

A modification of the von dem Borne suspension immunofluorescence test was used to identify antibodies to platelets in patients' serum.[10] The test uses "target" normal platelets incubated with patients' serum and then reacted with a fluorescein-tagged goat antihuman globulin (Cooper Biomedical). This tagged antihuman globulin was directed to the Fc portion of IgG. A thawed specimen of serum drawn from patient 5 (Table 1) during convalescence was also tested against autologous platelets obtained three years after recovery (day 1,076), when the platelet count was normal.

TABLE 1.—*Pertinent Data From 7 Patients With Epstein-Barr Virus-Induced Infectious Mononucleosis and Significant Thrombocytopenia*

Case	Age, yr	Sex	Clinical Findings	Lowest Platelet Counts, $\times 10^9$/liter*	Platelet Antibodies Found in Serum	Therapy	Follow-up Platelet Counts, $\times 10^9$/liter*
1	1	♂	Generalized lymphadenopathy; petechiae, extremities; ecchymoses, knees	15 (2)	No	None	520 (10)
2	2	♂	Generalized lymphadenopathy and palpable splenomegaly; petechiae, face and buttocks; ecchymoses, knees and elbows	9 (7)	No	None	161 (20)
3	7	♀	Cervical and inguinal lymphadenopathy; ecchymoses, extremities	25 (4)	ND	None	255 (12)
4	13	♀	Fever, sore throat; cervical lymphadenopathy; petechiae, generalized; heavy menses	8 (6)	No	Prednisone, 1 mg/kg/d	200 (20)
5	19	♂	Cervical lymphadenopathy, sore throat; petechiae, generalized; ecchymoses, feet	3 (7)	Yes, days 7, 34†‡	Prednisone, 1 mg/kg/d; platelet transfusions	239 (21)
6	24	♂	Fever, sore throat; cervical lymphadenopathy; petechiae, generalized; epistaxis	3 (6)	Yes†	Prednisone	452 (11)
7	63	♀	Flulike symptoms, sore throat; petechiae, legs; bullae, mouth	7 (13)	No	None	297 (27)

ND = not done

*Numbers in parentheses represent days after illness began.
†Late serum specimens from cases 5 (day 1,076) and 6 (day 2,415) did not show platelet antibodies.
‡A serum specimen from day 34 failed to react with autologous platelets in a specimen drawn on day 1,076.

TABLE 2.—*Pertinent Laboratory Data From 7 Patients With Epstein-Barr Virus (EBV)-Induced Infectious Mononucleosis and Significant Thrombocytopenia*

Case	After Disease Began, days	Hemoglobin, grams/liter	Leukocyte Count, $\times 10^9$/liter	Lymphocytes (Atypical), %	Peak AST Level, U/liter	Heterophil Titers		Anti-EBV Titers*			
						GPK	Beef	VCA IgM	VCA IgG	EA	EBNA
1	5	122	16.0	81 (35)	13	<7	<7	80	10	<10	2
	21	96	7.0	62 (4)	16	<7	<7	40	160	40R	10
2	7	113	9.9	55 (12)	ND	224	<7	160	320	40D	<2
3	14?	125	9.5	57 (11)	80	112	<7	ND	640	ND	ND
	42?	ND	ND	59 (8)	ND	56	<7	ND	ND	ND	ND
4	6	141	10.3	73 (50)	61	448	28	40	640	10D	5
5	7	145	9.7	55 (24)	78	7	14	160	1,280	<10	10†
	34	ND	9.7	15 (0)	ND	7	56	20	320	<10	5†
	1,076	156	6.7	42 (2)	ND	<7	<7	<10	640	<10	40
6	6	136	6.8	61 (>25)	650	57,344	7,168	640	640	160D	<2
	2,415	163	3.3	44 (ND)	ND	<7	<7	<10	640	20R	40
7	14	127	11.4	68 (26)	46	1,792	<14	160	320	20R	<2
	36	135	7.3	ND	56	112	<7	160	320	10R	<2

AST = aspartate aminotransferase, GPK = guinea pig kidney, Ig = immunoglobulin, ND = not done

*Serologic testing was done for antibodies to the following antigens: early antigen (EA), either D (diffuse) or R (restricted) type; EBV-associated nuclear antigen (EBNA); and viral capsid antigen (VCA).
†Interpretation limited due to the presence of antinuclear antibodies in serum.

Results

The pertinent clinical and laboratory data for the seven patients with severe thrombocytopenia are presented in Tables 1 and 2. Diagnostic difficulty was encountered especially in cases without prominent lymphadenopathy or with no heterophil antibody responses. An initial diagnosis of acute leukemia was made in two cases (1 and 7) and idiopathic thrombocytopenic purpura in three cases (3, 4, and 5). Usually EBV-induced infectious mononucleosis was subsequently considered a more likely diagnosis after substantial numbers of atypical lymphocytes were detected in peripheral blood smears. Serum aspartate aminotransferase levels were mildly elevated (46 to 80 units per liter) in four cases, at moderate levels (650 units per liter) in case 6, and within normal limits (13 units per liter) in case 1. Liver function studies were not done in case 2. Serum bilirubin values were within normal limits in all specimens from the five cases tested. Six cases were evaluated in a routine hospital laboratory for antinuclear antibodies and three for rheumatoid factors, with negative results in all instances. Cold agglutinins (4°C) were identified in three cases: as anti-i (1:112) in case 6, as anti-I (1:448) in case 2, and as neither anti-i nor anti-I (1:224) in case 5. No residual activity was noted in any of these cases at 25°C. Cold agglutinins were not detected in the other four cases. The results of a direct antihuman globulin test were negative in cases 1, 5, and 7, and the prothrombin or partial thromboplastin times were within normal limits in cases 1, 2, 3, 5, and 6.

Thawed serum specimens taken during the thrombocytopenic or acute phase of illness revealed antiplatelet antibodies against group O donor platelets in two of the six cases tested (5 and 6, Table 1). Follow-up specimens from these two patients drawn three and eight years later no longer contained platelet antibodies. Also, an additional thawed serum specimen taken during convalescence (day 34) from patient 5 reacted against normal donor platelets but, surprisingly, did not react against autologous platelets drawn 1,076 days after onset. Bone marrow specimens from patients 1, 5, and 6 showed normal cellularity with increased numbers of megakaryocytes and no granulomas. Acute-phase plasma specimens from eight additional 1986 patients with proven EBV-induced mononucleosis and platelet counts varying from 94 to 144 $\times 10^9$ per liter were also tested for antiplatelet antibodies with negative results.

Prednisone alone was administered to two patients (4 and 6) with severe thrombocytopenia and in conjunction with platelet transfusions to a third (5). Patient 5 received six units of donor platelet concentrates twice over a 12-hour period with no significant platelet count increment noted an hour after transfusion. The other four patients with thrombocytopenia received no specific therapy. All patients, regardless of treatment, had recovery of platelets without serious hemorrhagic complications.

Discussion

Thrombocytopenia complicating infectious mononucleosis is a phenomenon that has been long recognized although sparsely reported in the medical literature. Downey and McKinlay's landmark article, written more than 65 years ago, notes clinical findings suggestive of thrombocytopenic purpura in one of nine students suffering from "acute lymphadenosis."[11] Epistaxis and hematuria associated with glandular fever were noted even earlier.[12,13] Minot, in 1929, was the first to actually report significant thrombocytopenia—a platelet count of 25 $\times 10^9$ per liter—in a patient with infectious mononucleosis.[14] The coexistence of these two disorders raised concerns about the possibility of acute leukemia in the past.

Early attempts at determining a cause of symptomatic thrombocytopenia noted in a young man with infectious mononucleosis resulted in the identification of a serum factor that agglutinated group O donor platelets in vitro.[15] Based on differential absorption testing, this factor appeared to be different from the heterophil antibody. Since then, several cases of thrombocytopenia with infectious mononucleosis have been reported, in many of which an increased number of megakaryocytes in the bone marrow and a rapid response to steroid therapy were recorded, suggesting an autoimmune peripheral platelet consumption similar to the findings seen in idiopathic thrombocytopenic purpura.[16-25] The coexistence of Coombs'-positive hemolytic anemia and thrombocytopenia in other cases of infectious mononucleosis added corroborative evidence of an immune-mediated process.[26,27]

Clancy and co-workers noted transient abnormalities of platelet function in all of 16 patients who had infectious mononucleosis with normal platelet counts.[28] They suggested either nonspecific immune complexes or an immune reaction against a virus-platelet complex as possible causes of platelet dysfunction. Platelet autoantibodies were also identified from the IgG fraction of serum by a radioactive serotonin release test in a case described by Ellman and associates.[29] Subsequently, platelet antibodies have been identified by various other methods, including antiglobulin consumption,[27,30] platelet factor III release,[31] migration inhibition,[32] platelet lysing,[33] and an enzyme-linked immunospecific assay technique.[34-37] Immunofluorescent techniques have also been used with varying degrees of success to detect both free circulating antibodies and platelet-bound immunoglobulin.[25,37,38]

In the present study, we used an indirect immunofluorescence method modified from that described by von dem Borne[10] to identify antiplatelet antibodies in serum from two of six patients with EBV-induced mononucleosis and severe thrombocytopenia. While the presence of serum antibodies reactive in vitro against a panel of normal donor platelets is usually used as evidence of the presence of autoantibodies, the possibility that this test result indicates an alloantibody must always be considered. Such alloantibodies may be directed against either platelet-specific antigens or more ubiquitous systems such as the human leukocyte antigen. The development of such an alloantibody is a practical consideration in persons who have previously received blood transfusions or in multiparous women. In this study, both patients with tests positive for antiplatelet antibodies were young men (19 and 24 years of age, cases 5 and 6) who had had no previous transfusions. Patient 5, however, did receive platelet transfusions during the acute episode of thrombocytopenia, and this event makes the test results in this patient difficult to interpret. The failure of his early convalescent serum (day 34) to react with autologous platelets can possibly be explained in two ways:

- The antibody was actually an alloantibody that had been passively transfused with the platelet transfusions re-

ceived at the time of acute thrombocytopenia and was present in serum specimens from days 7 and 34.

- The antibody present in the acute-phase (day 7) serum was an autoantibody that disappeared rapidly with the return of a normal platelet count. By day 34, the patient had made an alloantibody to an antigen he was exposed to in the transfused platelets, which three years later had decreased to undetectable levels.

Because there was an insufficient amount of acute-phase serum left to test against autologous platelets, distinguishing alloantibody from autoantibody cannot be done with certainty.

Why only two of the six patients with severe thrombocytopenia tested had identifiable serum antiplatelet antibodies is not entirely clear. No clinical features in these two patients' courses appeared distinctive from the others; neither had substantially palpable splenomegaly. The two patients with positive test results had the lowest platelet counts—3×10^9 per liter—encountered during this study, but their results are probably not significantly different from those of the other five patients described due to the limits of reproducing platelet counts in that range. Possible explanations for the negative results include relatively complete adsorption of serum antibody to platelets, a loss of antibody activity over prolonged periods of serum storage, or circulating immune complexes (including antibody-viral complexes) that may not be identified in the testing system used in this report. Because this study was carried out retrospectively, we were unable to evaluate these cases for platelet-bound immunoglobulin; however, it is thought that the mechanism of thrombocytopenia in all of these cases is immune peripheral destruction, primarily in the spleen. It may well be that a more sensitive test for platelet-bound immunoglobulin of all major classes done on fresh specimens will detect considerably more cases of infectious mononucleosis with immunologically based thrombocytopenia.

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Medical Progress

Managing Malignant Pericardial Effusion

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The involvement of the pericardium by metastatic tumors is not uncommon, particularly in patients with lung cancer, breast cancer, lymphomas, leukemias, and melanomas. There are five therapeutic modalities for the treatment of malignant pericardial effusion, including pericardiocentesis, pericardial sclerosis, systemic chemotherapy, radiotherapy, and surgical treatment. The optimal treatment selection is dependent principally on a patient's life expectancy; responsiveness of the tumor to chemotherapy, irradiation, or both; and whether or not cardiac tamponade is present at diagnosis. The overall prognosis of patients with malignant pericardial effusion is primarily influenced by the extent and histologic features of the underlying cancer. Although this condition is usually incurable, a reasonable period of useful palliation can be obtained in most patients.

(Buzaid AC, Garewal HS, Greenberg BR: Managing malignant pericardial effusion. West J Med 1989 Feb; 150:174-179)

The development of a malignant pericardial effusion in patients with disseminated malignancy is not uncommon. The incidence ranges from 5% to 53% in autopsy and clinical studies and varies with the histologic diagnosis.[1-8] Because most patients are asymptomatic, the incidence is much higher in autopsy series.[8-10] The most common tumors to involve the pericardium are lung, breast, lymphomas, leukemias, and melanoma. They account for approximately 75% of malignant pericardial effusions that are clinically diagnosed.[10-16] Nevertheless, any tumor can potentially involve the pericardium and result in an effusion.[17]

Malignant pericardial effusion often has an insidious clinical onset that can mimic the picture of disseminated carcinomatosis. Occasionally pericardial involvement may be the first clinical manifestation of an undiagnosed malignant tumor.[18-23] Recognizing its presence is particularly important because of the life-threatening potential of cardiac tamponade. Furthermore, in a review of 55 patients with cancer who had pericardial disease, Thurber and co-workers found that pericardial involvement resulted in or contributed significantly to the cause of death in 85% of patients.[9] Thus, therapeutic interventions directed at controlling this complication of malignancy can, if successful, result in prolonging survival. The overall survival and quality of life of patients with malignant pericardial effusion is dictated primarily by the histologic type and extent of the underlying malignant process. For instance, in three recent large series where patients were treated surgically or with pericardial sclerosis, those with non-small-cell lung cancer had a median survival of approximately three to four months, whereas those with breast cancer had a median survival exceeding nine months.[24-26]

Because about 40% of patients with a symptomatic pericardial effusion and an underlying cancer may have nonmalignant pericardial disease,[27] determining the specific cause is of critical importance.[28] In this respect, special attention should be given to those patients who have received prior irradiation to the precordium because the treatment and prognosis of radiation-induced pericarditis are notably different.[29-33] The differential diagnosis should also include idiopathic pericarditis,[34] drug-induced pericarditis,[35] infection,[36] hypothyroidism,[37] and autoimmune disorders.[37,38] In this report we will not discuss the approach to establishing a specific diagnosis but will focus on the management of patients with a known diagnosis of malignant effusion and outline a treatment plan.

Because criteria for response vary among series, a direct comparison of the results of each therapeutic modality is not possible. In the few larger series, however, the criteria outlined by Smith and associates were usually used.[39] These are as follows: a decrease or disappearance of pericardial effusion lasting 30 days or more assessed by radiography and clinical examination; an absence of symptoms of pericardial tamponade for more than 30 days; and no requirement for pericardiocentesis 30 days after the initiation of local or systemic treatment. In more recent reports, echocardiography has been included to augment the accuracy of evaluating response.

Currently there are five major methods of treating malignant pericardial effusion: pericardiocentesis, pericardial sclerosis, systemic chemotherapy, radiotherapy, and surgical treatment. The overall treatment plan depends on several factors such as the presence of hemodynamic compromise, the general medical condition of a patient, expertise available at a particular institution, and the extent and histologic features of the tumor. The last clearly has a major effect on the prognosis.

Pericardiocentesis

The major indications for pericardiocentesis are to relieve an impending cardiac tamponade and to palliate symptoms. It also provides important information in patients without a confirmed diagnosis. For this purpose, pericardial fluid should be sent for blood cell and differential counts,

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TABLE 1.—*Intrapericardial Tetracycline Sclerosis in the Treatment of Malignant Pericardial Effusion*

Source	No. of Patients Improved/Total (%)	Mean No. of Instillations Required	Recurrence	Median Survival, days	Side Effects
Davis et al, 1984[25]	30/33 (90)	2.8 (range 1-7)	0	106 (range 28-704)	Fever in 12 patients; 1 episode of atrial fibrillation
Shepherd et al, 1985,[59] 1987[60]	43/58 (74)	2.9 (range 1-5)	3 (5%)	168 (range 30-1,149+)	Fever in 5 patients; pain in 9; transient atrial arrhythmia in 5; 1 patient had cardiac arrest before tetracycline instillation

TABLE 2.—*Technique for Tetracycline Sclerosis of Malignant Pericardial Effusion*

- Do echocardiographically guided pericardiocentesis with an 18-gauge catheter using a standard subxiphoid approach*
- Connect the catheter to a Hemovac suction system to drain for 12 to 24 hours
- Repeat echocardiography to check if the pericardial sac is "dry" (optional)
- Instill 5 ml of 2% lidocaine hydrochloride mixed in 10 ml of normal saline solution 20 minutes before tetracycline instillation
- Preadminister medication—50 to 75 mg meperidine hydrochloride intravenously or equivalent narcotic—before sclerosis procedure
- Instill 500 to 1,000 mg of tetracycline mixed in 20 ml of normal saline solution into the pericardial sac
- Clamp the catheter for 2 hours following tetracycline instillation, then allow it to drain to the Hemovac system
- Repeat the procedure every 24 to 48 hours until the net pericardial drainage is 25 ml or less in 24 hours
- Repeat echocardiography before removing the catheter to exclude loculation

*This is best done in a critical care area with the availability of electrocardiographic monitoring and resuscitative equipment.

lactic dehydrogenase, total protein, and glucose values, and cytologic study.[40-42] Although the results of cytologic study are abnormal in about 80% of cases, an additional test that appears to be useful is measuring the carcinoembryonic antigen levels in the pericardial fluid.[43]

The standard methods of pericardiocentesis use a subcostal blind puncture or an electrocardiographically guided procedure. Although these techniques may be appropriate in patients with life-threatening cardiac tamponade, they are associated with significant morbidity and mortality, including arrhythmias; damage and perforation of the myocardium; damage to the coronary, pericardial, or internal mammary arteries, leading to hemopericardium, hemothorax, and arteriovenous fistulas; pneumothorax; and, more rarely, damage to the liver with leakage of blood or bile.[34,44-47]

Recently Callahan and associates described the use of two-dimensional (2-D) echocardiographically directed pericardiocentesis.[48,49] They reported 132 consecutive procedures carried out in 117 patients. Complications were usually minor and never fatal. In one patient who previously had a right pneumonectomy for lung cancer, a symptomatic pneumothorax developed during the infiltration of a local anesthetic, while another had vasovagal syncope during needle insertion and refused to continue the procedure. In two patients, the right ventricular cavity was entered with a small sheathed needle (16 gauge), but the procedure was completed in both without complications.[49] Similar results have been obtained by Clarke and Cosgrove using real-time, echocardiographically guided pericardiocentesis.[50] In contrast to these data, complication rates of pericardiocentesis using either the blind or electrocardiographically guided techniques have been in the range of 7% to 15%,[44-47] with a mean mortality rate of 6% (range 0% to 19%) in five large series.[34,44-47] Furthermore, the 2-D echocardiographically guided pericardiocentesis can be used in patients who cannot assume a supine position because of dyspnea. In this group of patients, the pericardiocentesis can be done with the patient sitting upright. Another advantage of echocardiographic guidance is that it may occasionally show tumor masses infiltrating the myocardium or protruding from the pericardium or the epicardium into the echo-free space of the pericardial effusion, thus further supporting its malignant origin.[51-54] For these reasons, whenever possible, it should be the procedure of choice for pericardiocentesis.

Although pericardiocentesis alone can produce prolonged palliation in some patients,[55,56] additional therapy is usually necessary to ensure adequate control in most patients, particularly in those with a relatively long life expectancy.

Pericardial Sclerosis

Despite the wide acceptance and considerable experience with sclerosing agents in the treatment of malignant pleural effusion,[57] their use in patients with malignant pericardial effusion is much more limited.

The largest published experience has been with tetracycline, originally reported by Davis and co-workers.[58] Both their series[25] and the University of Toronto's recent update[59,60] are summarized in Table 1. The most important steps of this technique are described in Table 2. The overall results of both series were similar, with high efficacy and rare recurrences. Three instillations of tetracycline were usually required for optimal results. Although the reported complications were generally minor, in the Toronto series one patient had a cardiac arrest before the tetracycline instillation. To prevent major complications, the insertion of the pericardial catheter should always be done in an intensive care unit. The patient can then be transferred to a general medical ward, but special attention should be directed at accurately recording the pericardial drainage, analgesia, and monitoring of possible cardiac arrhythmias. The mechanism of action of tetracycline is still not completely understood. Analogous to the situation with malignant pleural effusions, it has been speculated that tetracycline can destroy mesothelial cells because of its high acidity (pH 2.0 to 3.0) leading to an inflammatory process and consequent pericardiodesis.[61,62]

Many other agents have been used for pericardial sclerosis including mechlorethamine hydrochloride, 5-fluorouracil, bleomycin sulfate, thiotepa, quinacrine hydrochloride, talc, and radioactive gold.[56,63-68] It is difficult to assess their efficacy because their use has been described principally in case reports.

Although the best indications for intrapericardial tetracycline sclerosis are not clearly defined, its application has increased significantly in the past few years, especially in institutions where the availability or experience with the sur-

gical management of malignant pericardial effusion is more limited. Regardless, we strongly favor the use of pericardial sclerosis in the following cases:

- Patients who present with cardiac tamponade or a substantial symptomatic pericardial effusion who require urgent pericardiocentesis to relieve an impending tamponade. In these patients, the catheter used for pericardiocentesis should be left in place for subsequent pericardial sclerosis.
- Patients who do not have either chemotherapy- or radiotherapy-sensitive tumors, especially those who are poor surgical candidates.

Systemic Chemotherapy

Although data concerning the role of systemic chemotherapy in the treatment of malignant pericardial effusion are limited, they do suggest that cytotoxic therapy may be effective in chemotherapy-sensitive tumors such as lymphomas, leukemias,[8,69-71] and occasional solid tumors.[72,73]

Acquatella and colleagues used echocardiography to prospectively evaluate 32 patients with non-Hodgkin's lymphoma[8] and showed that 17 (53%) had pericardial effusions. Of these, four patients with lymphoblastic lymphoma and extensive mediastinal involvement had clinical and echocardiographic signs of cardiac tamponade. Most patients were treated with CHOP—cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone—or modified-CHOP chemotherapy. The four patients with cardiac tamponade had an initial pericardiocentesis and, in addition to the chemotherapy, received palliative irradiation to the mediastinum. Of the 17 patients, 12 (70%) had complete disappearance of the pericardial effusion, including the 4 patients with cardiac tamponade. Although the follow-up period was short, the presence of a pericardial effusion had no effect on overall survival rates (70% with and 68% without pericardial effusion alive at one year).

Reynolds and Byrne[73] reported on three patients with malignant pericardial effusion due to breast cancer in whom control of the effusion was achieved with a single pericardiocentesis followed by intensive systemic chemotherapy. No patient required reaspiration or any other form of local treatment.

Recently Mufti and associates reported the efficacy of antileukemic therapy in four patients with malignant serous effusions due to acute monocytic leukemia.[69] Of these, one patient had pericardial effusion and had pronounced improvement with systemic chemotherapy alone.

Despite the paucity of published reports regarding the use of systemic chemotherapy in managing malignant pericardial effusion, the limited information available supports its use in previously untreated patients with highly chemotherapy-sensitive tumors. It can be used alone if there is no evidence of tamponade or combined with pericardiocentesis if tamponade is present.

Radiotherapy

The use of cardiac irradiation alone in the management of malignant pericardial effusion has received little attention in the literature. There are two published series of external irradiation, and their results are shown in Table 3.[74,75] As expected, radiotherapy was particularly effective in tumors known to be radiosensitive such as Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic leukemia, and breast cancer.[70,71,74-77]

A different form of radiotherapy was reported by Martini and co-workers from the Memorial Sloan-Kettering Cancer Center (New York)[78]: 28 patients with malignant pericardial effusion were treated by the intrapericardial instillation of radioactive chromic phosphate (^{32}P). Of these, 20 had no further problems with pericardial effusions after the initial tap and ^{32}P instillation. Eight required one additional pericardiocentesis one to five months later. Despite its apparent efficacy, this technique has been practically abandoned because of difficulty in handling the radioactive material, the expense, and the availability of other techniques capable of producing similar results.[66]

Radiotherapy is often recommended for patients with radiosensitive tumors such as lymphomas and leukemias.[39,66] However, because these tumors are also responsive to initial chemotherapy[8,69-71] and the malignant pericardial effusion usually represents a manifestation of widely metastatic disease, chemotherapy should precede radiotherapy if feasible. We recommend cardiac irradiation primarily in two clinical situations:

- Patients refractory to chemotherapy and who have radiosensitive tumors—such as lymphomas, leukemias, small-cell lung cancer, testicular cancer.
- Patients for whom sclerosis or a pericardial window fails and who are poor candidates for a second invasive procedure—that is, a second pericardial window or pericardial sclerosis—especially those with radiosensitive tumors.

Surgical Treatment

In the past five years, the surgical treatment of malignant pericardial effusion has become more popular, with more than 200 cases having been reported.[24,79-90] The results of recent surgical series are summarized in Table 4. Most pa-

TABLE 3.—*Treatment of Malignant Pericardial Effusions With Radiotherapy Alone*

Source	*Histologic Diagnosis*	*No. of Patients Improved/Total (%)*	*Duration of Improvement, mo*
Terry and Kligerman, 1970[74]	Hodgkin's disease	4/4 (100)	2,* 9, 12, and 25
	Lymphoblastic lymphoma	1/1 (100)	10*
	Chronic myeloid leukemia	1/1 (100)	10*
	Lymphosarcoma	1/1 (100)	1*
Cham et al, 1975[75]	Breast carcinoma	11/16 (69)	2-36 (median 4)
	Lung cancer†	2/7 (28)	1 and 9
	Lymphoma and leukemia	6/7 (86)	2-4
	Miscellaneous	4/8 (50)	1-4

*All patients died without evidence of recurrence of the pericardial effusion.
†Histologic subtype not specified.

tients underwent a pericardial window, usually done with the patient under general anesthesia. In general, surgical treatment was effective and recurrences were rare. Early deaths after the operation (within 30 days) were usually due to the underlying cancer and were not uncommon. This emphasizes the importance of suitable patient selection with special attention to the prognosis of the underlying malignant tumor.

The surgical treatment of malignant pericardial effusion may be accomplished with a subxiphoid approach, a left anterior thoracotomy, or a median sternotomy. Although treatment selection is strongly influenced by the experience with each procedure at a particular institution,[79] the subxiphoid approach should probably be the procedure of choice because, compared with the other surgical modalities, it is at least as effective and can be done using local anesthesia with overall lower morbidity and mortality.[82,91] On the other hand, a left anterior thoracotomy, which is still the predominant approach in certain institutions, has the advantage of allowing better exposure of the pericardium and can yield a larger amount of material for diagnostic studies. Nevertheless, it should be reserved for patients who are good surgical candidates because it requires general anesthesia and is associated with higher morbidity.[79] In this setting, to prevent hypotension from the induction of anesthesia, it is recommended that these patients undergo pericardiocentesis before the operation.

Technically, the subxiphoid pericardial window is a relatively simple procedure that can even be done with the patient in a semisitting position in patients who cannot lie supine because of dyspnea. The major steps involved in this technique are shown in Figure 1. Relative contraindications for a subxiphoid approach, particularly if using local anesthesia, include extreme obesity, a narrow costal angle, and a previous midline abdominal operation.[86]

Patients with constrictive pericarditis represent a distinct group. Constrictive pericarditis may be due to extensive tumorous thickening of the pericardium or irradiation to the precordium. In both cases, an extensive pericardial resection through a median sternotomy is probably the best approach in view of the high incidence of late constrictive pericarditis in cases managed with a simple pericardial window.[24,80] Because extensive pericardial resection is associated with significant morbidity and mortality, however, it should be indicated with caution in patients with a poor prognosis and active malignancy and reserved principally for those with radiation-induced constrictive pericarditis who are probably cured of their cancer.[79]

The following are the major indications for surgical intervention:

- Patients with malignant pericardial effusion and anticipated long survival, particularly those for whom irradiation, pericardial sclerosis, or both, have failed.

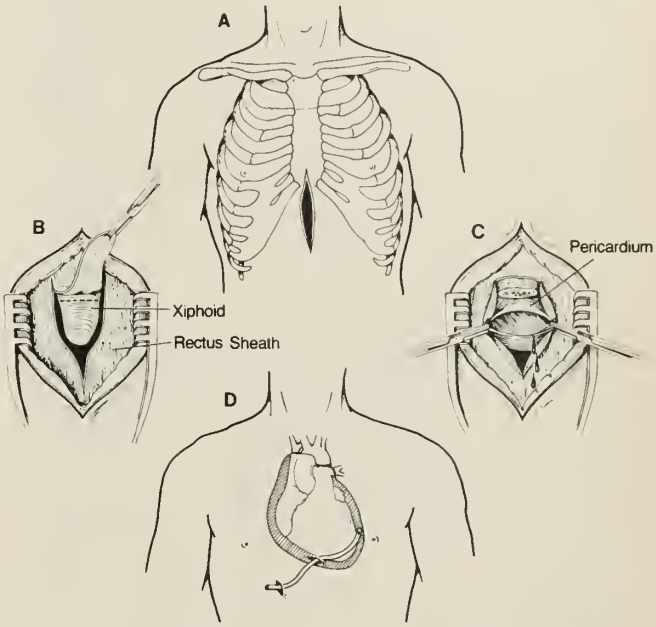

Figure 1.—The subxiphoid technique for creating a pericardial window is shown. **A,** A midline incision is done. **B,** The xiphoid process is removed to provide maximal access to the substernal space. **C,** The pericardium is grasped with clamps and a window is created. **D,** A thoracic catheter is inserted along the inferior aspect of the pericardium.

TABLE 4.—*Surgical Treatment of Malignant Pericardial Effusion*

Source	*No. of Patients Improved/Total (%)*	*No. of Recurrences (%)*	*No. of Patients Who Succumbed to Cancer Within 30 Days After Operation (%)*	*Comments*
Piehler et al, 1985[24]	70/72 (97)	3 (4)*	14 (20)	3 recurred at 2.5, 3, and 3.5 months; 23% alive at 1 year
McKenna et al, 1985[79]	44/49 (90)	3 (7)	7 (14)	44 underwent pleuropericardial window
Miller et al, 1982[80]	26/26 (100)	0	3 (11)	3 who died early all had lung cancer; 19 had breast cancer with 15 alive > 1 year
Gregory et al, 1985[81]	18/25 (72)	3 (17)	At least 3 (16)	3 recurred at 4, 5, and 6 months
Ghosh et al, 1985[82]	20/20 (100)	Not stated	Not stated	Some patients had the procedure under local anesthesia
Hankins et al, 1980[83]	17/17 (100)	0	6 (35)	2 alive at 8 and 21 months
Osuch et al, 1985[84]	12/12 (100)	0	Not stated	Average survival was 6.7 months
Little et al, 1984[85]	6/6 (100)	0	4 (67)	All received irradiation to the pericardium after the procedure; 2 alive at 9 and 11 months
Prager et al, 1982[86]	5/6 (83)	0	Not stated	5 deaths occurred within 43 days after operation
Alcan et al, 1982[87]	5/5 (100)	0	Not stated	2 patients died in hospital; 3 patients also had tetracycline sclerosis
Hill and Cohen, 1970[88]	3/4 (75)	1 (33)	0	1 recurred at 13 months; 2 patients received irradiation to the pericardium after the operation
Berman et al, 1984[89]	3/3 (100)	0	0	Procedure done using local anesthesia
Liepman and Goodlerner, 1981[90]	2/2 (100)	0	0	Both patients had acute leukemia

*Two cases that recurred within 4 weeks were considered primary failures and not recurrences in this analysis.

• Patients with an underlying malignant tumor and a pericardial effusion who may have benign pericardial disease, such as radiation-induced pericarditis.

• Patients with pericardial effusion, probably malignant in nature, who lack adequate histologic confirmation of malignancy, and a tissue diagnosis is otherwise difficult to obtain.

• Selected patients with a long life expectancy and constrictive pericarditis due to tumorous involvement of the pericardium and patients with radiation-induced constrictive pericarditis.

Conclusions

The literature regarding the management of malignant pericardial effusion is still limited. Major treatment options include pericardiocentesis alone or more often combined with another modality such as pericardial sclerosis, systemic chemotherapy, cardiac irradiation, or surgical treatment. After the diagnosis of a malignant pericardial effusion is firmly established, a treatment approach should be outlined taking into consideration the patient's life expectancy, whether or not the tumor is sensitive to chemotherapy or radiation therapy, and whether or not the patient presents with cardiac tamponade.

Because of the relatively small size of most series, the heterogeneous study population, not infrequently the concomitant use of multimodality treatment, and varying criteria for a clinical response, stringent recommendations concerning the optimal use of each therapeutic modality are not possible. The treatment selection especially between sclerosis and a pericardial window is also influenced by the experience with each therapeutic modality at a particular institution.

Our suggested approach to managing malignant pericardial effusion is as follows:

• Patients with a symptomatic, malignant pericardial effusion, a long life expectancy (more than three months), without cardiac tamponade, whose tumor is not very sensitive to chemotherapy or radiotherapy, such as non-small-cell lung cancer, and who are good surgical candidates may be considered for an elective subxiphoid pericardial window. We would emphasize that this recommendation is dependent on the availability and experience with this surgical approach at each institution. A suitable alternative would be pericardial sclerosis, which, in fact, is the preferred approach in many institutions regardless of the surgical condition of the patient. If cardiac tamponade or significant symptoms are present at diagnosis, pericardiocentesis with subsequent sclerosis using the same catheter is the best initial approach. Pericardial sclerosis should also be considered for those who are poor surgical candidates, such as patients with severe chronic obstructive pulmonary disease.

• Patients with malignant pericardial effusion, no prior chemotherapy, and who have chemotherapy-sensitive tumors (lymphomas, leukemias, small-cell lung cancer, or testicular cancer) should receive systemic chemotherapy. If significant symptoms or cardiac tamponade is present, a pericardiocentesis to relieve symptoms should precede the chemotherapy. Radiotherapy should be considered if chemotherapy fails to control the effusion.

• Patients with malignant pericardial effusion and a short life expectancy (a month or less) should probably undergo only pericardiocentesis. If frequent pericardiocenteses become necessary, sclerosis should be considered.

• Patients with a history of malignancy who may have benign pericardial disease that cannot be diagnosed by other means, or those with a probable malignant pericardial effusion but who lack histologic confirmation of the type of malignancy and there is difficulty in obtaining a tissue diagnosis from other sites should undergo an operation for diagnosis and treatment.

In choosing a therapeutic plan, it must be remembered that the overall prognosis of patients with malignant pericardial effusion is primarily dictated by the histologic type and extent of the underlying cancer. Except for a few malignant diseases such as lymphomas and leukemias, involvement of the pericardium virtually always reflects incurability. Nevertheless, a nihilistic attitude towards the management of malignant pericardial effusion is not justified because for many patients a reasonable period of meaningful palliation can be obtained.

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Clinicopathologic Conference

Seizures and Hemiparesis in a Young Woman 24 Years After Treatment of Astrocytoma

Discussants and Contributors

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An edited transcript of Neurology Grand Rounds held at the University of California, Los Angeles, Medical Center on January 27, 1988. John Mazziotta, MD, PhD, Professor of Neurology and Radiology, is the coordinator of these conferences. This conference was edited by Harry V. Vinters, MD.

(Mazziotta JC, Jordan SE, Lones M, et al: Seizures and hemiparesis in a young woman 24 years after treatment of astrocytoma [Clinicopathologic Conference]. West J Med 1989 Feb; 150:180-186)

JOHN C. MAZZIOTTA, MD*: A 32-year-old woman known to have had a right parietal astrocytoma resected in 1963 and 1976 was seen because of increased seizure frequency, inattention, and left-sided weakness. The patient's neurologic problems began in childhood. While being evaluated for a "limp" with hip radiographs, she experienced her first seizure at age 2 years. This seizure and subsequent ones consisted of the following phenomena: tonic followed by tonic-clonic movements of the left foot spreading to the leg and arm on the left side without loss of consciousness, postictal lethargy, or weakness. The patient had an electroencephalogram (EEG) and a pneumoencephalogram, the results of which were suggestive of, but not diagnostic for, an abnormality in the right cerebral hemisphere posteriorly. A surgical exploration was not done, and therapy with phenytoin (Dilantin) was started. She continued to have about one seizure per month but otherwise developed normally.

In mid-1963 the patient's pediatrician noted slight weakness of the peroneal muscles of the left leg and slight left foot inversion on walking. In November 1963 the patient had the development of a left foot drop associated with an increased frequency of seizures. Following one typical seizure the patient had a flaccid left hemiparesis, was difficult to arouse, and had an intermittently dilated right pupil. On examination, she also had bilateral extensor plantar signs and a "cracked pot" sign on skull percussion. Skull x-ray films showed erosion of the right parietal and frontal bones manifested by thinning of the inner table of the skull and erosion of the dorsum sellae. Angiography showed a right parietal mass, and the diagnosis of a right parietal brain tumor with incipient transtentorial herniation was made.

The patient had a right parietotemporal craniotomy and subtotal excision (a volume of 50 to 60 ml) of a grade II astrocytoma. After the operation the patient had 45 Gy (4,500 rads) of cobalt 60 irradiation from lateral opposing ports over 36 days. On discharge from the hospital, her right arm was still weak and the left leg was paralyzed. Her medication was switched from phenytoin to phenobarbital. Over the next nine years, the patient had about one focal seizure per month and normal technetium brain scans. Atrophy and spasticity of the left lower extremity required a tendon operation in 1972.

In mid-1976 a computed tomographic (CT) scan showed a cystic contrast-enhancing mass in the right frontoparietal region, with bowing of the falx from right to left. A second frontoparietal craniotomy was done with removal of a recurrent grade II astrocytoma. After the operation the patient received cobalt 60 radiation therapy with 40 Gy delivered to the tumor site and border zone and an additional 10 Gy to the tumor site itself. Phenytoin therapy was restarted. From 1976 until the present admission, the patient continued to have some degree of left leg and arm weakness.

During adult life, her seizures have been characterized by an awareness of an impending event, vibratory sensation in the left thigh that spreads to the left arm, occasional incontinence, and then focal motor movements of the left side excluding the face. The patient occasionally experienced loss of consciousness and noted that the seizures typically occurred more often in the early morning. Her seizures continued at intervals of approximately every six months. In the early 1980s her phenytoin dose was reduced because of gingival hypertrophy, and primidone (Mysoline) was added.

In November 1987 the patient deteriorated neurologically, resulting in her readmission to UCLA Medical Center. A week before admission her seizure frequency had increased to every other day and then to every day, with two events becoming secondarily generalized to major motor seizures. Her primidone dose was doubled—250 mg twice a day—but this failed to provide adequate anticonvulsant protection. On the day of admission, the patient had three seizures and noted increased weakness of her left side.

On admission, the patient said she had not recently had

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
EEG = electroencephalogram
MRI = magnetic resonance imaging
SPECT = single photon emission CT
UCSF = University of California, San Francisco

fever, chills, nausea, vomiting, diarrhea, or any other neurologic symptoms not noted above. She did note that she had an upper respiratory tract infection about two weeks before admission and had been having occasional headaches for the month preceding admission. There was no family history of neurologic, neurocutaneous, or epileptic disorders. The patient had completed college but had never been employed. She said she did not use alcohol or nonprescription drugs.

On physical examination (November 1987), the patient had temporal alopecia and scars from the previous right-sided craniotomies and left leg operation. Carotid artery and facial pulsations were normal. Her skin was free of neurocutaneous lesions. There was left-sided atrophy, pronounced in the lower extremity and mild in the upper extremity. There were no other abnormal physical findings.

On mental state examination, the patient was oriented but slightly inattentive, needing to be reminded of questions at times but always responding appropriately. Her language was fluent but somewhat slurred. Comprehension and repetition were normal. The patient had some difficulty with abstract concepts but otherwise her mental state testing did not reveal focal abnormalities.

The results of a cranial nerve examination were normal (including her visual fields) with the exception of the following: blurring of the lateral optic disc margins and absence of retinal venous pulsations. In addition, there was weakness of the left eye closure.

The motor examination was notable for decreased muscle mass on the left side with the leg more involved than the arm, a bilateral increase in tone of a spastic nature (greater on the left than the right), and a left pronator drift. The left ankle was maintained in a flexed position. Strength on the right was normal. Strength on the left was 0/5 for wrist and finger extensors, wrist flexors, toe extensors and flexors, and the tibialis anterior; left gluteal strength was 3/5; quadriceps, finger flexors, gastrocnemius, and iliopsoas were 4−/5; and the deltoid, biceps, and triceps were 4/5 on the left side.

Coordination testing showed mild slowing of rapid alternating movements on the left, normal finger-to-nose movements, and the absence of tremor or involuntary movements.

Sensory testing showed normal perception of temperature, pain, position, vibration, stereognosis, and graphesthesia on the right side of the body and face. Normal vibration and position sense, stereognosis, and graphesthesia were noted on the left, but there was decreased perception of light touch and pinprick on the left side of the body and decreased temperature sensation in the left leg. When sensory stimuli were presented simultaneously to both sides of the body, she did not perceive them on the left side.

Tendon reflexes were normal on the right side and increased on the left (left/right: brachioradialis 3+/2, biceps 3+/3, knee 3+/3, ankle 2/2). Bilateral palmomental reflexes were elicited, and an extensor plantar response was noted on the left but not on the right side. The patient did not have glabellar, snout, or grasp reflexes.

Laboratory studies showed normal values for the following: platelet count, electrolytes, blood urea nitrogen, phosphorus, calcium, magnesium, glucose, bilirubin, liver function tests, total thyroxine, and thyroid-stimulating hormone. An electrocardiogram and a chest radiograph were also normal. Her complete blood count had normal indices, cell and differential counts, but a low hematocrit of 0.33. A urinalysis revealed trace blood and protein. Anticonvulsant medication concentrations were as follows: phenytoin, 9 μg per ml, and primidone, 7 μg per ml. An EEG showed continuous polymorphic right central and temporal slowing with an intermittent right frontotemporal spike focus.

In the hospital the patient had a CT scan that showed a right frontoparietal contrast-enhancing mass about 2 cm in diameter (Figure 1). Magnetic resonance imaging (MRI) (Figure 1) showed generalized cerebral atrophy and postsurgical changes on the right with generalized edema and residual soft tissue fullness. A single photon emission CT (SPECT) study using thallium Tl 201 showed uptake of the isotope in the right frontal region. A procedure was done.

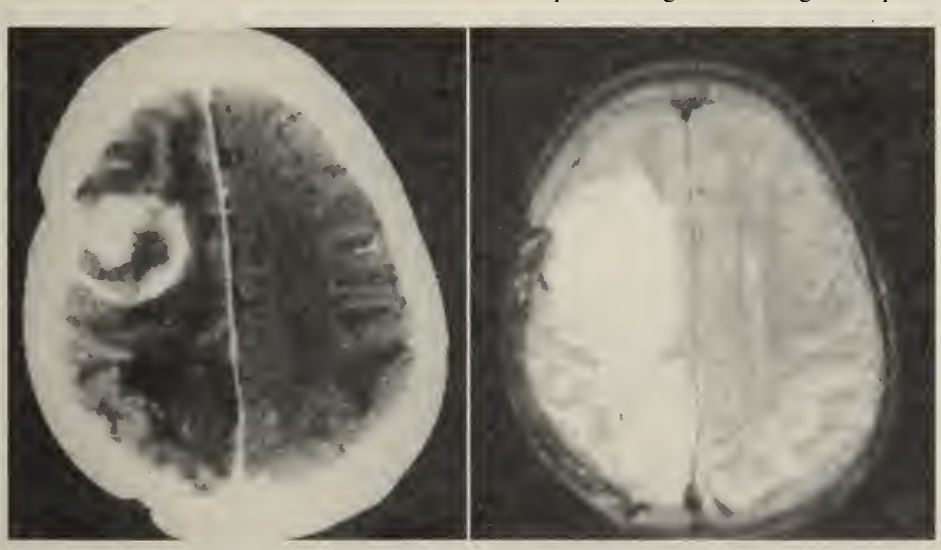

Figure 1.—Left, A cerebral computed tomographic scan from the most recent admission shows a contrast-enhancing mass in the right frontal lobe with some edema. **Right,** A magnetic resonance imaging scan of the brain shows vasogenic edema extending throughout the right cerebral hemisphere.

SHELDON E. JORDAN, MD*: This case shows the present state of neurologic diagnosis. We have one foot in the 19th century and another trying to get into the 21st. The 19th-century foot stands on classical techniques of diagnosis based on the interpretation of signs and symptoms that are elicited at the bedside. With reference to the 21st century, we hope that the development of imaging techniques will be helpful in giving us more diagnostic specificity, possibly without the need for more invasive techniques such as biopsy.

First, consider this patient's problems, in particular the seizure disorder. She had clonic activity of the left leg spreading to the left arm but sparing the face. On occasion, particularly late in the patient's course, it became generalized. The occurrence of focal tonic-clonic seizure activity suggests involvement of the sensorimotor cortex. The seizures began in the left area of the motor cortex, so a lesion would be expected near the dorsomedial precentral cortex.

As to the hemiparesis, apparently this was an old problem because the patient had atrophy, presumably on the basis of disuse, and also had contractures of some of the joints. Most of this hemiparesis may relate to the cerebral astrocytoma that was originally found in the right cerebral hemisphere. Again, it appears that the leg was involved more than the arm, which in turn was involved more than the face.

Considering the topography of motor function in the cortex, analysis of the hemiparesis suggests localization consistent with the seizure problem—that is, the lesion can be localized in the dorsomedial aspect of the precentral area, the lateral ventral area of the rolandic cortex being relatively spared.

Considering the sensory alterations, the patient had altered pin, light touch, and temperature perception out of proportion to deficits in graphesthesia and stereognosis. There was extinction to bilateral simultaneous stimulation indicating involvement of the right parietal cortex. Nevertheless, graphesthesia and stereognosis were thought to be relatively preserved. The latter sensory modalities are frequently impaired when the cortex is damaged. The overall pattern of sensory deficits suggests that there was injury to the thalamus or thalamocortical projections, with at least partial sparing of the parietal cortex.

To assess the pathophysiologic features of the case, the classic teaching has been to look at additional features, such as the temporal profile of symptom evolution. During the two weeks before the December 1987 admission, the patient had a notable worsening in the intensity and frequency of seizures despite the fact that at least one of the anticonvulsants was at a therapeutic serum level. This is consistent with the temporal profile typically found with a rapidly growing tumor, radiation necrosis, or an abscess and appears to be too slow for a typical stroke.

Analyzing the associated signs gives additional information. The patient had evidence of early papilledema. There was a loss of venous pulsations and bulging forward of the disc margins, the last suggesting that there was a mass lesion. The finding of papilledema makes it unlikely that the patient's worsening over the last weeks was due to a demyelinating process. A rapidly growing tumor, radiation necrosis with associated edema, and abscess are all still clinical possibilities, but an abscess is unlikely. Although the patient had a brief flulike syndrome, she has not had any other evidence of infection such as a pneumonia, sinusitis, or other process that might predispose her to a localized cerebral infection.

In summary, the patient had a lesion in the right frontoparietal region with some involvement of the hemispheric white matter, perhaps as deep as the thalamus. The motor cortex was involved as noted by the seizures, and there was evidence of both gray and white matter disease, rapidly progressive over the course of two weeks. A prime consideration is that of a rapidly growing tumor. This patient was said to initially have had an astrocytoma, grade II. The worsening course over a week or two is more rapid than one would expect for progression if this were still a low-grade astrocytoma. The patient may have a more malignant tumor evolving, such as a transformation of the original tumor to a higher grade (III or IV) astrocytoma.

The EEG findings in this case are not diagnostically specific, but at least they appear to confirm what may be occurring based on the bedside examination. The patient had polymorphic delta activity in the right central region. This suggests that there was involvement at or immediately below the cortex in the right hemispheric white matter. Spikes in the frontal and anterior temporal region suggest that there was cortical involvement of these regions. Again, there appears to be evidence of gray and white matter disease that localizes to the right frontoparietal region.

As to the MRI scan data, without contrast media like gadolinium to evaluate the breakdown of the blood-brain barrier or the development of hypervascularity, the MRI scan in this case does not provide much diagnostic specificity. Crowding of the sulci of the right frontoparietal region was seen, compared with relative atrophy of the sulci in the opposite hemisphere. An area of encephalomalacia was identified in the right frontal region. Relatively T2-weighted images showed increased signal in the hemispheric white matter extending from the frontal region to the occipital region. The latter change may be largely related to her previous radiation dose, a total of 90 Gy. There did not appear to be distortion, abnormal signal change, or thickening of the corpus callosum that might suggest infiltration of glioma across the midline.

In summary, the MRI scan confirms what we already know about the case: there is a mass in the right frontoparietal region. We are unable to differentiate radiation necrosis from a recurrent low-grade glioma or from a recurrent high-grade glioma, abscess, or other type of mass lesion.

The CT scan in this case may provide more diagnostic specificity than the MRI scan. First, consider the typical features that are seen with low-grade gliomas. One common pattern seen on CT scans of low-grade gliomas before a contrast medium is given is the presence of calcification in clumps or in a scattered punctate distribution. There may be an inconspicuous hypodense region on the precontrast scans, and the postcontrast scans may show no enhancement. Another common finding is that of a cystic lesion, in which case there may be a small contrast-enhancing nodule along the wall of the cyst. Another common CT scan presentation is that of a patchy, ill-defined area of low density on precontrast scans without a cyst or calcification. After a contrast medium is given, scans may show patchy, ill-defined enhancement. In contrast to low-grade gliomas, higher grade gliomas such as glioblastoma more frequently have an intense ring enhancement pattern or a more clear-cut nodular pattern on the postcontrast scan.

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The CT scans of this patient did not show the patchy, ill-defined enhancement patterns typical of a low-grade glioma. Rather, this patient's postcontrast scan showed an intense, well-defined enhancement pattern more typical of a higher grade tumor. Radiation necrosis, however, can show ring enhancement on CT. Therefore, the differential diagnosis is between a high-grade tumor and radiation necrosis.

The SPECT scan using a thallium radionuclide provides more specificity in this case than was available with any of the other imaging tests. This shows an intensely dark area in the right frontal region that appears to correspond to the contrast-enhancing area on the CT scan. It also corresponds to where the localization would be expected based on the bedside analysis. Such findings on a thallium SPECT scan are typical for a high-grade glioma. The experience with other high-grade malignant tumors is limited with this technique, so the possibility of a radiation-induced sarcoma cannot be excluded.

In short, based on the neuroimaging findings, we can narrow our differential diagnostic list to a malignant tumor occurring in an area where the patient previously had a low-grade glioma and radiation therapy. Radiation necrosis appears unlikely. Although a positron emission tomographic scan was not done, I suspect that the results would be similar to those obtained with the SPECT scan.

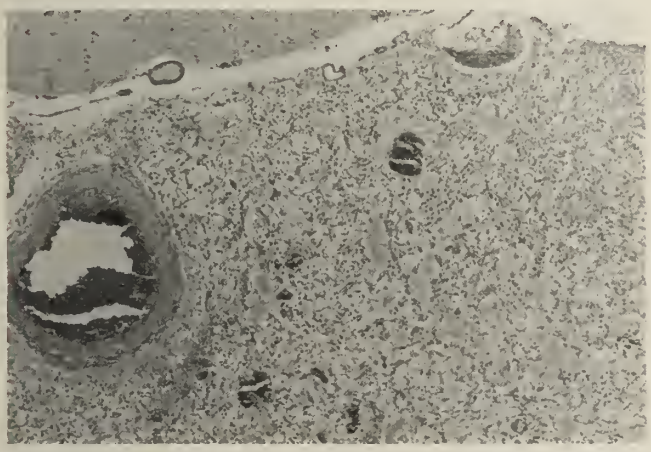

Figure 2.—Histologic sections from the initial surgical resection (1963) show some normal cerebral tissue (upper left corner) and a neoplasm composed of uniform nuclei with minimal atypia, a fibrillary background, and microcystic regions with amorphous material. Normal vascular structures are present and no mitoses are identified (hematoxylin and eosin, original magnification × 75).

MARK LONES, MD*: The patient's original right cortical tumor resection was done in November 1963 and yielded semitranslucent white-pink soft tissue. Histologic sections show normal cerebral tissue and a uniformly hypercellular lesion composed of uniform nuclei with minimal atypia, a fibrillary background, and microcystic architecture with amorphous eosinophilic material (Figure 2). Normal blood vessels are seen, and mitotic figures are inconspicuous. These findings are diagnostic of a low-grade astrocytoma (grade II).

The next surgical resection at the same site was done in July 1976. This yielded a mass of hemorrhagic material containing light yellow edematous tissue with a glistening mucoid appearance, with a total weight of 34 grams. Sections show a histologic appearance similar to that of the original tumor (Figure 3). In addition, there are areas of tissue necrosis, fibrinoid necrosis of vessels, hyalinization of vessels, and microcalcification. Many of these changes—such as necrosis and vascular change—appear due to the previous irradiation.[1] The recurrent tumor is also an astrocytoma (grade II).

The gross appearances of the patient's most recent tumor were those of a firm, tan-white, and brown mass with no apparent attachment of tumor to bone. Histologic sections show a uniform, notably hypercellular neoplasm nearly entirely composed of spindle-shaped cells in a fascicular pattern (Figure 4) with large areas of necrosis. There are multiple areas of irregularly shaped hyaline pink material surrounded by the atypical cells. These areas represent the formation of malignant osteoid with focal calcification (Figure 4). The spindle-shaped cells show elongated atypical nuclei with blunted ends, and numerous mitotic figures are seen in a single high-power field. These findings are diagnostic of osteogenic sarcoma or osteosarcoma.[2]

The possibility of gliosarcoma—that is, a mixed glioma and sarcoma—was considered, and an immunohistochemical stain for glial fibrillary acidic protein was done on sections of tumor using a peroxidase-antiperoxidase procedure. Sec-

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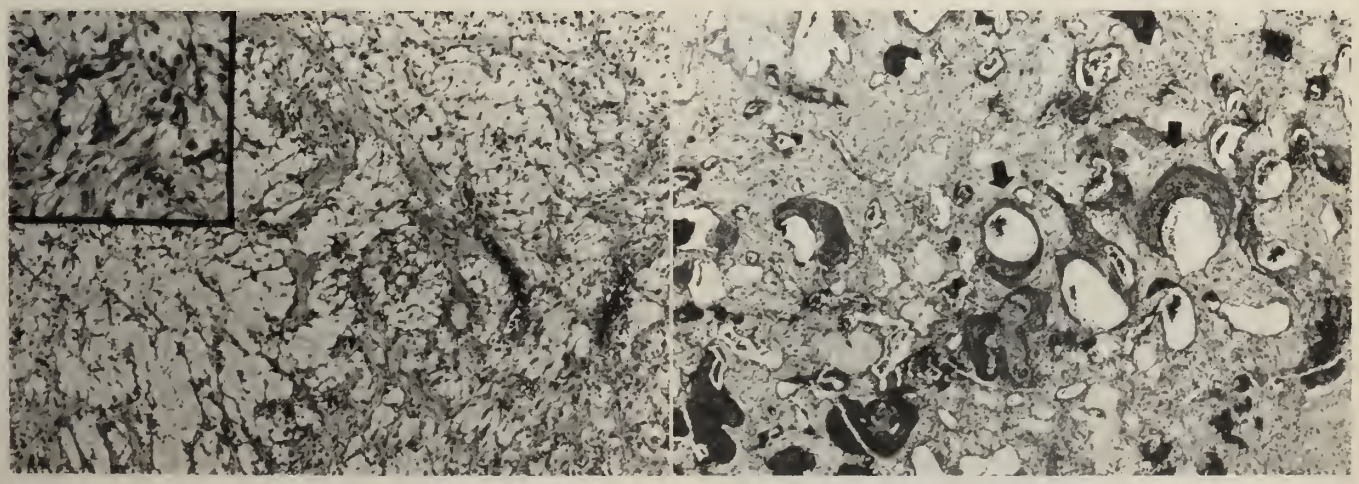

Figure 3.—Sections of the recurrent astrocytoma (1976) show **(left)** a tumor similar in histologic appearance to the tumor originally resected (original magnification × 190). The inset shows a detail of the nuclear features (× 495). **Right,** in addition, fibrinoid necrosis of vessels **(arrows)** is present (× 75; in all, the stain is hematoxylin and eosin).

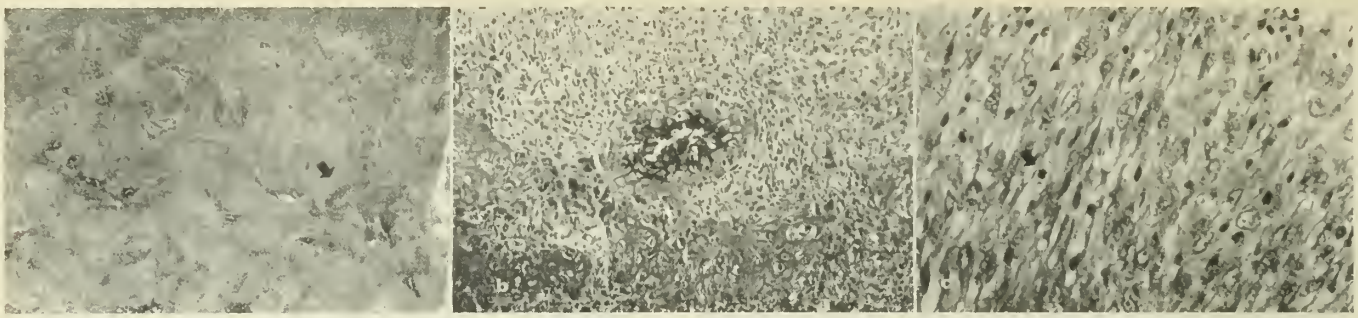

Figure 4.—Histologic sections of the most recent surgical specimen show a spindle cell neoplasm in a fascicular pattern with **(a)** many areas of irregularly shaped osteoid formation **(arrow)** with some calcification (original magnification × 24); **(b)** details of the osteoid are seen (× 190); **(c)** the spindle cells contain atypical elongated or oval nuclei with blunt ends, and mitoses are prominent **(arrow)** (× 495; in all, the stain is hematoxylin and eosin).

tions showed no glial elements within the neoplasm, but rare reactive astrocytes were present at the periphery of the lesion. Representative portions of this neoplasm were submitted for evaluation by electron microscopy. Sections showed plump tumor cells with eccentrically placed nuclei, prominent nucleoli, and abundant rough endoplasmic reticulum (Figure 5) in a fibrillary and collagenous matrix, characteristics consistent with osteosarcoma but not in themselves diagnostic.[3]

The criteria used to make the diagnosis of radiation-induced sarcoma have been described by Arlen and co-workers.[4] These include the following:

- The malignant neoplasm must have different histologic features from the primary lesion, benign or malignant;
- The sarcoma must arise within the radiation field;
- A long latent period must be present between radiation therapy and sarcoma diagnosis; and
- There must be histologic proof of sarcoma.

These criteria are fulfilled in our patient.

A review of the literature on postradiation osteosarcomas of the skull shows a few large series of case reviews and several case reports.[4-13] Most cases have occurred in the orbit of patients with retinoblastoma given radiation therapy. There are more than 70 such cases, as reviewed by François.[6] Other large reviews include only a few tumor sites in the skull. A recent clinicopathologic study includes nine cases of skull osteosarcoma (locations: calvaria, 2; orbit, 1; maxilla, 2; mandible, 4).[7] Two other large reviews of postradiation sarcoma[10,13] include 16 cases of sarcoma of the skull (calvaria, 5; maxilla, 7; mandible, 4).[13] The number of osteosarcomas of the skull is not reported in this review, however.[13]

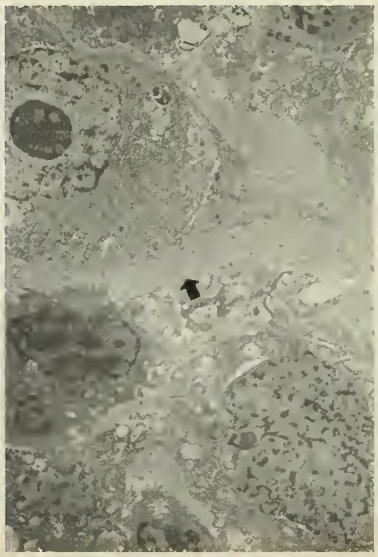

Figure 5.—An electron micrograph from a representative portion of tumor (most recent resection) shows round to oval cells with abundant rough endoplasmic reticulum. The extracellular matrix includes collagen **(arrow)**. A pyknotic cell is seen at the lower left corner (uranyl acetate and lead citrate, original magnification × 6,900).

Osteosarcoma following irradiation of pituitary adenomas has been described,[2,8,12] as has osteosarcoma of the calvarium after radiation therapy for an astrocytoma.[5] From these case reports and reviews, the critical radiation doses ranged from 20 to 260 Gy, and the subsequent latency periods from the end of radiation therapy until tumor occurrence ranged from 4 to 42 years. In the patient under discussion, the radiation dose was 95 Gy, and the latency period was at least 11 years.

Keith L. Black, MD*: I will make several comments regarding ^{201}Tl SPECT scanning. To date, we have studied about 30 patients with brain tumors using this technique. There appears to be a correlation based on our preliminary data between abnormal findings on scans and patients with grade III and IV primary gliomas. Evidence in the literature suggests that ^{201}Tl scanning is a sensitive method for observing recurrence of tumor, the thallium scan showing tumor recurrence before either CT or MRI scans.[14] The fact that this patient had an abnormal scan suggested that her lesion represented a high-grade recurrence of the previous lesion rather than radiation necrosis.

Because our primary working diagnosis was that of a recurrent high-grade primary brain tumor, the patient was being considered for a third craniotomy with redebulking of her tumor and the placement of carmustine (BCNU) biodegradable polymers into the tumor cavity. However, the rapid decline in the patient's neurologic state due to increased intracranial pressure necessitated an urgent craniotomy with debulking of her lesion.

At the operation, a firm and fibrotic mass similar to a meningioma was found arising from the dura. There was no involvement of the overlying skull, and the tumor could be readily dissected to form a clear plane between the mass and the underlying brain parenchyma. The brain under the mass was gliotic but was not involved with the neoplastic process. Grossly, the tumor was totally excised, and a wide dural margin was achieved. A dura patch graft was placed, and after the operation the patient did well, with improvement of her mental state as well as of strength in her lower extremities so that she was again able to ambulate with a walker.

The dramatic abatement of her neurologic symptoms correlated most with a resolution of the vasogenic edema sur-

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rounding the neoplasm. Typically after a gross total excision of a highly permeable lesion, there is a remarkable resolution of the surrounding edema and mass effect, allowing the patient to have a significant neurologic improvement. Because the final pathologic diagnosis was found to be an osteosarcoma, the patient was also considered for chemotherapy after her surgical resection.

MICHAEL T. SELCH, MD*: Three questions need to be addressed. First, why was the patient irradiated after her initial operation? The role of postoperative irradiation in the management of partially resected, low-grade astrocytomas remains controversial. Nevertheless, a body of literature supports the administration of radiation therapy in this situation. Leibel and colleagues at the University of California in San Francisco (UCSF) have shown, albeit in a nonrandom fashion, a longer survival of patients with incompletely resected, low-grade astrocytomas given radiation therapy compared with patients undergoing only partial resection.[15] This survival benefit accrued to patients with both grades I and II astrocytomas, to adult and pediatric patients, and to those with tumors in all cerebral sites. Moreover, a longer survival for the irradiated patients was shown even in those followed as long as 20 years after treatment. Despite the better survival following irradiation, however, continued tumor relapse was noted in this group of patients. This suggests that radiation therapy does not always prevent the recurrence of a partially resected low-grade astrocytoma. Rather, radiation therapy significantly delays such a recurrence. A similar improvement in the survival of patients with partially resected, irradiated, low-grade astrocytomas has been shown in other retrospective reviews.[16,17] In view of these accumulated data, many of them available in the 1960s, I think the radiation oncologist was justified in treating this patient following her initial operation.

Radiation therapy in a patient with an incompletely resected, low-grade astrocytoma should be delivered to a partial brain field that includes the neoplasm plus a margin of uninvolved parenchyma as determined by CT and MRI scans.[18] Because these advanced studies were unavailable before 1976, designing partial brain fields using the neuroradiologic tools of this patient's era may have been difficult. Many studies show an underestimation of the gross and microscopic extent of high-grade astrocytomas when partial brain fields are outlined using only a pneumoencephalogram, angiogram, and isotope scan.[19-21] Such tumor volume underestimation was possible with a case of low-grade astrocytoma in the era before CT and MRI scans. The radiation oncologist treating this patient in 1963 cannot be faulted if a volume approaching whole brain had been treated even though retrospective data from the Mayo Clinic indicate no influence of the irradiation field size on survival in the treatment of such patients.[18] The initial dose delivered is entirely appropriate because there is no evidence to support doses in excess of 45 to 55 Gy in a patient with an incompletely resected low-grade astrocytoma.[15,18]

The second question involves more art than science. Why was this patient *re*irradiated? Few data are available to radiation oncologists considering the retreatment of a brain tumor. In this difficult situation, they are often forced to rely on personal philosophy coupled with anecdotal experience. Several clinical features in this case suggest that the basic decision to embark on a second course of therapy was a rational one: the patient showed a favorable response, as measured by the time to relapse, to the initial course of irradiation; the histologic diagnosis at the time of relapse remained low-grade astrocytoma, which is potentially controllable for a prolonged period; the initial course delivered a tolerable dose by conventional fractional increments; at the time of relapse, the patient was still young and in a good functional state; and the recurrent lesion could be irradiated using a restricted portal size.

Once the decision to reirradiate was made, a second full course of irradiation was more logical than delivering a low palliative dose. In the UCSF experience with partially resected low-grade astrocytomas cited earlier, the authors noted that the delivery of doses of less than 35 Gy produced long-term survival that was no better than that following only partial resection.[15] According to Dritschilo and associates, patients with irradiated brain tumors who relapse more than three years after therapy can be considered to have recovered radiation tolerance such that a second full dose can be delivered.[22] In the literature, when the aforementioned criteria are satisfied, occasional long-term disease-free survival is possible following the reirradiation of brain tumors.[22,23]

The final question concerns the differential diagnosis of the lesion bringing the patient to UCLA in November 1987. Three possibilities must be entertained: recurrent astrocytoma, central nervous system damage due to radiation therapy, and a radiation-induced malignant tumor. Recurrent astrocytoma is possible because postoperative radiation therapy does not always prevent relapse, and this patient has already experienced one relapse. Certainly, reirradiation would be unlikely to be more successful than a primary course of therapy. The recurrent tumor could be either low or high grade. The latter situation, it must be stressed, is not necessarily a consequence of the previous radiation exposure triggering de-differentiation of a low-grade astrocytoma. Rather, as Müller and co-workers have shown, the phenomenon of a low-grade astrocytoma relapsing as anaplastic astrocytoma or glioblastoma is part of the natural history of low-grade tumors, whether irradiated or not.[24]

Central nervous system damage due to irradiation ("brain necrosis") is also a likely possibility in this patient considering the cumulative dose delivered. The actual incidence of brain necrosis following various total dose and fractionation regimens remains unknown because the number of patients at risk is unknown. Only overt cases of brain necrosis appear in the literature, and these cluster around doses of 55 to 60 Gy or more delivered in 1.8- to 2.0-Gy fractions. From this clinical experience, the conventional tolerance of the brain—that dose associated with a 5% or less complication rate—is assumed to be 60 Gy delivered in conventional fractions.[25] It is further known that the total dose that the brain can tolerate very much depends on the size of dose per fraction and relatively less so on the overall time taken to deliver a given dose.[26] For example, delivering a total dose of 60 Gy to the brain in 2.0-Gy fractions over 6 weeks will be no more damaging to the brain than the same total dose in 2.0-Gy fractions delivered over 12 weeks. A corollary is that prolonging the overall treatment time ("split course" therapy) is not necessarily protective to the brain. Even when the split is measured in years—as it is with reirradiation—there is no proof that the human brain can tolerate cumulative doses

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beyond 60 Gy. Despite the conclusion of Dritschilo and associates regarding the reestablishment of brain tolerance after several years, recovery of normal parenchyma from the effects of ionizing irradiation cannot be assumed.[22] Because the relationship of dose to complication rate is sigmoidal in the organs for which radiation oncologists have data, it is likely the same relationship pertains to the central nervous system. In such a model, small increases in total dose can lead to substantial increases in complication rates. For all these reasons, a cumulative dose of 90 Gy could certainly produce brain necrosis. Brain necrosis is further suggested in this patient in view of the delay from her second course of therapy to her recent lesion. The clinical onset of brain necrosis peaks at one to two years following irradiation, but documented cases have been reported many years after treatment. In addition, while the CT scan rarely shows contrast enhancement in brain necrosis following 65 Gy or less, contrast enhancement is more likely when necrosis follows doses in excess of 65 Gy.

Finally, ionizing irradiation is known to be a weak carcinogen. Leukemias and malignant epithelial neoplasms such as thyroid cancer are known to follow low-dose exposure. Epithelial tumors are also rarely reported to be induced by therapeutic doses of irradiation used to treat various curable malignant disorders such as Hodgkin's disease and breast cancer. Malignant lesions of the central nervous system—especially meningioma and astrocytoma—have been reported following the prophylactic irradiation of the meninges in childhood leukemia or irradiation of primary brain tumors such as medulloblastoma.[27,28] Sarcomatous degeneration has also been associated with therapeutic doses of radiation therapy. If doses much larger than those traditionally associated with therapy are used, as is the case here, the risk of an induced sarcoma rises. Sarcomas following irradiation usually prove to be osteogenic sarcoma of bone or fibrosarcoma of soft tissue.[13,29] Sarcomas of the calvarium or brain parenchyma are generally rare following radiation therapy because the dose level commonly linked to sarcoma induction is not often applied to human brain tumors. Those primary brain lesions to which high radiation doses are occasionally delivered are generally associated with a short survival. These patients do not remain at risk long enough for a sarcoma to develop.

Those cases in the literature of calvarial osteogenic sarcoma or soft tissue sarcoma of brain following radiation therapy have usually been associated with irradiation of relatively indolent tumors such as pituitary adenoma or cerebellar astrocytoma.[5,12] The survival of such patients exceeds the long latency period associated with sarcoma induction by radiation therapy.

In closing, I call attention to two situations in which osteogenic sarcoma was apparently induced by moderate doses of irradiation. In the first instance, radiation therapy was combined with the administration of alkylating chemotherapeutic agents such as dactinomycin or cyclophosphamide. This class of antineoplastic agents appears to work synergistically with irradiation in inducing second malignant tumors, which explains the osteogenic sarcomas occasionally noted in survivors of Ewing's sarcoma.[30] In the second instance, osteogenic sarcoma follows irradiation that was delivered using x-rays in the kilovoltage range. Ionizing irradiation in this range deposits a far higher dose in bone compared with that calculated in soft tissues for reasons of basic physics. This phenomenon is often unappreciated when a radiation-induced sarcoma develops in a patient with a tumor irradiated before 1960.[31]

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Medical Staff Conference

The Adult Respiratory Distress Syndrome
New Insights Into Diagnosis, Pathophysiology, and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *For this Medical Staff Conference, we are pleased to have Dr Michael Matthay, Associate Professor of Medicine and Anesthesia and Associate Director of the Intensive Care Unit. He will discuss the adult respiratory distress syndrome.*

MICHAEL A. MATTHAY, MD†: The adult respiratory distress syndrome (ARDS) was first described in 1967. Although Petty and co-workers are correctly given credit for this description, a careful reading of Osler's textbook of medicine elicits an excellent description of the early phase of the syndrome. Osler wrote that "uncontrolled septicemia leads to frothy pulmonary edema that resembles serum, not the sanguinous transudative edema fluid seen in dropsy or congestive heart failure."[2] There were no mechanical ventilators or intensive care units in Osler's time, so he could not tell us more about ARDS because the development of this type of exudative pulmonary edema was usually a terminal complication. Since the adult respiratory distress syndrome was described more than 20 years ago, however, it has become a widely recognized, frequent cause of acute respiratory failure in patients treated both medically and surgically. In the early 1970s, the National Institute of Health began to invest heavily in both clinical and basic research to determine the epidemiology of ARDS and to identify the primary mechanisms of acute lung injury and repair with the overall goal of discovering more effective treatment.[3]

Now, 20 years later, it is time to ask, what have we learned? This question can be divided into three major issues. First, what have we learned about the diagnosis and the definition of the adult respiratory distress syndrome, and will our expanded (1988) definition of the syndrome contribute to a better understanding of its prognosis? Second, what have we learned about the pathogenesis and the pathophysiology of ARDS? Third, what is the status of current treatment, and what new treatment options are likely to be available in the future?

Expanded Definition of ARDS

First, let us examine the evolution in our definition and understanding of ARDS over the past 20 years. In 1967 Petty and colleagues described a syndrome of acute respiratory failure characterized by noncardiogenic pulmonary edema with severe hypoxemia caused by right to left intrapulmonary shunting through air spaces that were collapsed or filled with edema fluid.[1] The chest radiograph showed diffuse pulmonary infiltrates, and there was a decrease in lung compliance, meaning that the lungs required higher than normal airway pressures to inflate them. It was estimated in 1977 that there were about 150,000 cases of ARDS in the United States annually, with a mortality of at least 50% to 60%, although prospective studies had not yet been done.[3]

The original description by Petty and associates was useful but simple, and, in view of our current clinical understanding of the syndrome, the definition needs to be expanded. In the 1970s and early 1980s, a number of prospective clinical studies provided an increased recognition of the epidemiology of ARDS and the heterogeneous clinical patterns that may occur. Second, over the past five years, there has been a growing appreciation of the systemic manifestations of the disease. In particular, we have more insight regarding the contribution of multiorgan failure as a determinant of ultimate outcome. We also have a much better understanding of the clinical effects of infection on both the initial phase and the ongoing clinical course of patients with ARDS.

Recently investigators at the University of Colorado (Denver) and the University of Washington (Seattle) medical centers reported their data from prospective studies that were designed to determine the epidemiology of ARDS.[4,5] Both studies identified the sepsis syndrome and gastric aspiration as the two clinical disorders most commonly associated with ARDS (Table 1). Also, the risk of ARDS developing increased in parallel with the number of clinical disorders that occurred in the same patient. The University of Washington study examined the time course for the development of ARDS after the start of the clinical disorder. Overall, ARDS developed in 80% of the patients within 24 hours. Subsequently, a prospective study of 40 patients with sepsis was done at UCSF. In that group of patients, the time frame for ARDS developing after sepsis was less than six hours in many patients.[6] These findings had important implications. The original hope was to intervene with treatment that would attenuate acute lung injury before respiratory failure occurred. Clearly it will be more difficult to achieve

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
PEEP = positive end-expiratory pressure
UCSF = University of California, San Francisco
vWF = von Willebrand factor

this objective because the lag time between the start of the clinical disorder—that is, sepsis—and the development of acute respiratory failure is usually brief.

Another group of investigators at the University of Texas Health Science Center (Dallas) documented the importance of multiorgan failure in ARDS.[7] The associated systemic complications of ARDS were better described, including acute renal failure, gastrointestinal dysfunction, coagulation abnormalities, central nervous system dysfunction, and hepatic disease. The majority of patients with multiorgan failure had uncontrolled infection. Clinical and pathologic comparisons were possible because most patients who died had a postmortem examination. If a patient had clinical evidence of infection but the site of infection had not been identified before death, the source of infection was usually in the abdomen, providing that the patient had positive blood cultures. In contrast, when patients had negative blood cultures with clinical sepsis, the postmortem examination showed that the origin of the infection was usually in the lung.

TABLE 1.—*Incidence of the Adult Respiratory Distress Syndrome (ARDS) Following Clinical Risks**†

Clinical Condition	*Incidence of ARDS*	
	Washington‡	*Colorado*‡
Sepsis		
Bacteremia	...	9/239 (4)
Sepsis syndrome	5/13 (38)	...
Aspiration of gastric contents	7/23 (30)	16/45 (36)
Fracture	1/12 (8)	2/38 (5)
Multiple transfusions		
10 units/24 h	...	9/197 (5)
10 units/6 h	4/17 (24)	...
Cardiopulmonary bypass	...	4/237 (2)
Burn	...	2/87 (2)
Pneumonia in ICU	...	10/84 (12)
Disseminated intravascular coagulation	...	2/9 (22)
Pulmonary contusion	5/29 (17)	...
Near drowning	2/3	...
Pancreatitis	1/1	...
Prolonged hypotension	0/1	...

ICU=intensive care unit

*These data refer to patients with only a single risk event. Not included are those with multiple risks.
†Modified from Fowler et al[4] and Pepe et al.[5]
‡Data given as number of cases in relation to the number at risk (percent).

Another important study was published subsequently by Montgomery and co-workers from the University of Washington.[8] This study showed that the early and late mortality in patients with ARDS was related primarily to sepsis. The actual cause of death in the first three days after the beginning of ARDS was respiratory failure in only 10% of the patients. In fact, although the incidence of respiratory failure as a cause of death increased to 18% in those who died after three days, most of these patients had a complicating pneumonia. Thus, uncontrolled sepsis was the leading cause of death for both early and late mortality (Table 2).

Another recent study reported that the overall survival rate was actually only 29% in a group of 129 patients with ARDS.[9] Infection was much more common in nonsurvivors, and the lung and abdomen were the most common sites of infection. In addition, these investigators found that adequate antibiotic treatment did not favorably influence survival (Table 3). Thus, even when the patients received an appropriate course of antibiotics, the outcome was still poor.

In view of our growth in understanding both the systemic and pulmonary features of ARDS, Murray, Luce, and I have proposed an expanded 1988 definition of ARDS. We hope that this will be accepted nationally as a new standard for describing ARDS,[10] and we think that it will be useful to clinicians in community hospitals, as well as valuable for prospective clinical research.

The first part of the definition is based on a semiquantitative method for scoring acute lung injury. We developed this system a few years ago when studying the patients who were at risk for the development of ARDS from sepsis.[6] We tested the hypothesis that evidence of complement activation in the plasma of patients could predict which cases of sepsis would progress to ARDS. For the study to be done properly, at least a semiquantitative scoring system for the clinical severity of acute respiratory failure was needed. The scoring is based on a four-point system. First, the oxygenation defect is quantified by the ratio of the arterial oxygen tension to the fraction of inspired oxygen. Second, the chest radiograph is scored on

TABLE 2.—*Direct Causes of Death in Patients With the Adult Respiratory Distress Syndrome (ARDS) and Control Subjects**

Irreversible Dysfunction (Direct Cause)	*ARDS Group*				*Non-ARDS Group*			
	Early Mortality (n=10)		*Late Mortality (n=22)*		*Early Mortality (n=25)*		*Late Mortality (n=30)*	
	Number	*(%)*	*Number*	*(%)*	*Number*	*(%)*	*Number*	*(%)*
Sepsis	3	(30)	8	(36)	3	(12)	15	(50)
Cardiac	1	(10)	5†	(23)	1	(4)	1	(3)
Respiratory	1	(10)	4‡	(18)	..	(0)	2§	(7)
Central nervous system	3	(30)	4§	(18)	13	(52)	10	(33)
Hematologic status		(0)	1	(4)	3	(12)	1	(3)
Hemorrhagic shock	2	(20)	..	(0)	5	(20)	..	(0)
Hepatic		(0)	..	(0)	..	(0)	1	(3)

*From Montgomery et al.[8]
†Three patients had sepsis and respiratory dysfunction as a contributing cause, and one patient had respiratory dysfunction as an indirect cause.
‡Sepsis was present as a contributory cause in all patients.
§Sepsis was present as a contributory cause in one patient.

TABLE 3.—*Outcome Determinants in the Adult Respiratory Distress Syndrome**

Determinant	Patients, Number	Survivors, Number	Survivors, Percent
All study patients	129	37	29
Infection			
Present	108	23	21†
Absent	21	14	67
Antibiotic therapy‡			
Adequate	69	20	29§
Inadequate	13	3	23

*Adapted from Seidenfeld et al.[9]
†$P=.01$, χ^2 contingency analysis.
‡Not significant by χ^2.
§Includes patients with known site of infection only.

a four-point system. If the chest radiograph is clear, then no points are assigned. If there is interstitial edema, one point is assigned, and then increasing points are assigned up to a maximum of four for the degree of alveolar edema and the extent of lung involvement. A radiologist is not needed to grade the film. Third, respiratory system compliance can be calculated (if the patient has an endotracheal tube and is being given oxygen) by dividing the tidal volume by the plateau airway pressure minus the level of positive end-expiratory pressure (PEEP). Finally, it is important to factor in the level of PEEP for at least two reasons: PEEP affects oxygenation, and the level of PEEP required provides some indication of the severity of respiratory failure. With this four-point scoring system, we can classify acute lung injury as mild to moderate (0.1 to <2.5) and severe lung injury or overt ARDS (≥ 2.5). This scoring system has been very useful. In fact, in our first study of 40 patients with sepsis, we found that ARDS occurred in 20% of the patients, but 60% of the patients had mild to moderate lung injury.[6] Thus, these findings provided a more realistic view of the spectrum of the acute lung injury that occurs after sepsis.

The second part of the expanded definition specifies the clinical disorder(s) associated with ARDS. Table 1 provides a list of the most commonly associated disorders. The most lethal and most common cause of ARDS is the sepsis syndrome. It is important to specify the microbiology of the sepsis (gram-positive, gram-negative) and to indicate the anatomic source of the infection (lung, abdomen, urine, skin, intravenous catheter, and the like). Although the prognosis has not been specifically related yet to the specific source or type of bacterial infection, careful prospective studies may yet identify important differences in the prognosis of patients with the sepsis syndrome, depending on the specific infection and source. In fact, it was recently discovered that the source of sepsis has an influence on the sensitivity of plasma markers that may be useful to predict the development of ARDS. As mentioned earlier, we studied complement levels in the plasma of septic patients before the development of acute lung injury; neither C5a nor C3a plasma levels predicted the development of ARDS.[6] However, a new study of patients with sepsis has been done that examines plasma levels of von Willebrand factor (vWF) antigen, a product of endothelial cells.[11] Data have been prospectively collected from more than 70 patients. When all the patients with sepsis were examined together, the level of vWF antigen had no predictive value. When patients with nonpulmonary sepsis were analyzed, however, then the plasma level of vWF antigen had a 77% sensitivity and 90% specificity for predicting acute lung injury.

Aspiration is another clinical disorder frequently associated with ARDS. It is not adequate, however, simply to designate that a patient had gastric aspiration. One study, for example, reported the prognostic value of oxygenation data in patients who had suffered a witnessed episode of gastric aspiration.[12] The authors determined arterial blood gases on 44 patients within an hour after the witnessed aspiration. Then they calculated the ratio of arterial oxygen tension to the alveolar oxygen tension. If the ratio was 0.5 or less, then mortality was 48%; if the ratio was greater than 0.5, then mortality was 14% ($P<.05$).[12] Thus, by including the oxygenation data, we may be able to better assess the prognosis of patients with ARDS from gastric aspiration. Of course, the type of aspiration must be specified because it can include patients who have had near drowning with fresh or salt water or patients who may have inhaled or aspirated toxins.

Major trauma encompasses another large heterogeneous group of patients. The adult respiratory distress syndrome develops in some major trauma patients in association with lung contusion or within the first 24 hours of the trauma after severe hypotension, emergency surgical treatment, and multiple transfusions.[5] ARDS develops in others when they become septic a few days after trauma. In other patients, ARDS occurs following major trauma and long bone fractures from the fat embolism syndrome. The prognosis of ARDS from fat embolism is much better, however, than that of ARDS following sepsis or immediately after major trauma, hypotension, and surgical treatment.[13] Supportive treatment simply with mechanical ventilation should result in a greater than 90% survival in patients with ARDS after fat embolism.

A number of other clinical disorders may be associated with ARDS, including drug overdoses with aspirin and with heroin. These drugs may injure the lung directly. Patients who have drug overdose associated with the use of tricyclic antidepressants or barbiturates may have lung injury from the hypotension, concomitant gastric aspiration, or other factors that need to be specified. Cardiopulmonary bypass is another important cause of ARDS, though perhaps less common than in the past. In our experience at UCSF, the prognosis for ARDS following cardiopulmonary bypass is better than from other causes of acute lung injury.[14] As we use the expanded definition of ARDS, we will probably learn more about the specific causes of clinical lung injury and the relationship of the associated clinical disorder to prognosis.

Finally, the third part of the scoring system specifies the function of the nonpulmonary organs. We need to record the renal and acid-base status, any central nervous system deficits or hematologic abnormalities, and gastrointestinal and hepatic function. Cardiovascular abnormalities were overlooked in the early descriptions of ARDS. In fact, a requirement for the diagnosis of ARDS was that the patient not have cardiac disease. In a recent review of the clinical literature, however, as many as 20% of patients with acute ARDS were found to have concomitant cardiac disease.[15-17] Because patients with acute and chronic cardiac failure have a higher risk of infection, it makes sense that they may have a higher chance of ARDS developing. If we fail to specify a patient's cardiac function when ARDS is diagnosed, then interventions that are designed to treat the lung disease or the systemic manifestations of ARDS may not be effective because we are including patients with an especially poor prognosis

due to the associated cardiac disease. Mortality in patients with pulmonary embolism, for example, has been closely linked to the presence of cardiac disease.[18,19]

To provide an example of the value of this new classification system, consider the study published in 1985 by Fowler and co-workers.[20] These investigators reported that there were three variables at the beginning of ARDS that correlated with a particularly poor outcome. They found that patients with ARDS had a mortality rate greater than 80% if a patient's initial pH remained less than 7.4 (after being intubated and mechanically ventilated), if the serum bicarbonate level was less than 20 mmol per liter (20 mEq per dl), and if the initial blood urea nitrogen level was greater than 23 mmol per liter (65 mg per dl). The ARDS patients without these findings still had a 40% mortality, but clearly the patient groups were different, though both groups of patients had the diagnosis of ARDS. This is just one example of how systemic factors may influence outcome and how it may be valuable to characterize carefully a patient's clinical status to develop a reliable prognostic system. Table 4 summarizes the three major categories in the expanded definition of ARDS.

Pathophysiology and Pathogenesis

Briefly, what we have learned about the pathophysiology and pathogenesis of ARDS in the past 20 years is that we can divide ARDS clinically and pathologically into an acute phase, a subacute phase, and a chronic phase.[21] In early studies of ARDS, the exudative, protein-rich edema, usually with large numbers of neutrophils in the air spaces and interstitium of the lung, was described. Ultrastructural studies of the lungs of patients dying in the first 24 hours of the adult respiratory distress syndrome showed evidence of lung endothelial injury, presumably leading to the capillary leak and increased permeability pulmonary edema (Figure 1).[21,22]

As we know now, however, the magnitude of lung injury in the acute phase is more extensive than originally suspected. Although initially most investigators focused on injury to the endothelium, morphologic studies published by Bachofen and Weibel[21] in 1977 showed considerable epithelial injury in patients dying of ARDS (Figure 1). Protein-rich edema along with precipitated protein in the form of hyaline membranes and cellular debris is easily identified in the air spaces in the acute phase of ARDS (Figure 2).[22] Epithelial injury makes sense as an important factor in outcome because the epithelium is the final barrier that guards the air spaces and allows the lung to function for its major purpose, gas exchange. The findings of a recent clinical study at UCSF suggest that the presence or absence of normal alveolar epithelial function, as measured by sequential protein concentrations in edema fluid, may be an important prognostic indicator in ARDS patients.[14]

TABLE 4.—*Criteria for Expanded Definition of Acute Lung Injury*

Severity of Acute Lung Injury
Arterial oxygenation (Pa_{O_2}/Fi_{O_2})
Chest radiograph
Static lung compliance
Level of positive end-expiratory pressure
Associated Clinical Disorder(s)
Sepsis (microbiology, anatomic site)
Aspiration (type)
Major trauma
Drug overdose
Cardiopulmonary bypass
Systemic Organ Function
Acid-base status
Renal function
Hematologic abnormalities
Hepatic function
Central nervous system function

Fi_{O_2} = fraction of inspired oxygen, Pa_{O_2} = partial pressure of arterial oxygen

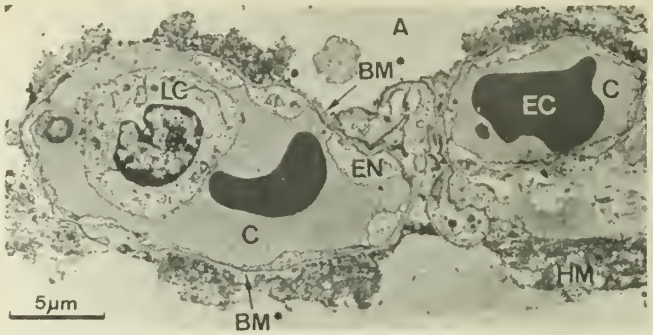

Figure 1.—An ultrastructural lung specimen shows the alveolar septum with extensive epithelial destruction in a 19-year-old woman who died after 4 days of fulminant capillary leakage due to septicemia. Note the irregularly swollen and damaged endothelium (from Bachofen and Weibel[22]). A = alveolar space, BM* = denuded basement membrane, C = capillary, EC = intravascular erythrocyte, EN = swollen endothelial cell, HM = hyaline membrane, LC = intravascular leukocyte

Figure 2.—An ultrastructural lung specimen from a 17-year-old woman, who died of complications that included the adult respiratory distress syndrome 3 days after a traffic accident, shows an alveolar entrance ring **(AER)** covered by a hyaline membrane **(HM)** composed of condensed plasma protein and fibrin strands **(F)**. Close contact of hyaline membrane to the epithelial basement membrane **(BM)** is restricted to an area of destroyed epithelial lamina (from Bachofen and Weibel[22]). A = alveolar space, C = capillary

Originally, airway abnormalities were not identified as an important feature of ARDS. A study of survivors of ARDS showed, however, that the patients who recovered from this disease had reasonable pulmonary function, but some had reactive airway disease with no previous history of smoking and no history of asthma.[23] Subsequent clinical studies of survivors of ARDS have confirmed a significant incidence of airway disease.[24] Also, experimental studies by Snapper and associates showed that *Escherichia coli* endotoxemia caused substantial airway constriction in sheep.[25] This bronchoconstriction was mediated by thromboxane and could be inhibited by cyclooxygenase blockade with indomethacin or meclofenamate sodium. The airway constriction occurred before interstitial or alveolar edema developed in these studies. Recently, Ploysongsang and colleagues have adapted the interrupter technique to measure airway resistance in patients with ARDS and have found that at least 50% of patients with established ARDS have substantial airway abnormalities.[26]

Finally, because of the work at UCSF by Wiener-Kronish and co-workers, we now know that even the pleural space is involved in ARDS.[27,28] Originally it was thought that the absence of pleural effusions was a requirement for the diagnosis of ARDS. Because most chest radiographs of ARDS patients are taken with the patients supine, moderate-sized effusions were missed. Using two-dimensional echocardiography, Wiener-Kronish and colleagues have found that most patients with ARDS have moderately large, sterile pleural effusions.[27] On the basis of their experimental work, we know that about 20% to 25% of the excess lung water of pulmonary edema that accumulates in the acute phase drains into the pleural space and is cleared from the thoracic cavity by pleural lymphatics.[28] Thus, the pleural space is not just a passive bystander; it participates in removing a substantial fraction of the pulmonary edema fluid.

What have we learned about the subacute phase of ARDS? In this phase (five to ten days after ARDS begins), some patients have an accelerated fibrosing alveolitis. There is an impressive proliferation of alveolar type II epithelial cells that provide a new epithelial lining, apparently in response to the death of the type I alveolar epithelial cells in the acute phase. Also, there is a pronounced increase in fibroblasts and collagen formation (Figure 3). The mechanisms for these responses to the acute lung injury are poorly understood, but there is considerable interest in the presence of fibroblast and epithelial growth factors that may be released from alveolar macrophages after acute lung injury.[29] In the subacute phase, there are fewer neutrophils and more lymphocytes, plasma cells, monocytes, and cellular debris in the air spaces.[22]

Finally, in the chronic phase, which begins pathologically about 14 to 20 days after the initial insult, there is variable lung destruction with emphysema and vascular obliteration along with areas of intense fibrosis (Figure 4).[21,22]

Briefly, what are the mechanisms that may explain acute lung injury? Microthrombi and fibrin deposition are frequently found in pathologic studies of patients with ARDS, as well as in various animal models of ARDS.[30,31] Many investigators have reported an association of disseminated intravascular coagulation with ARDS.[32] One group also reported substantial elevations of a fibrin or fibrinogen degradation product, D antigen, in the plasma of patients within 60 hours after the start of ARDS.[33] Further evidence of the importance of coagulation abnormalities in the development of acute lung injury came from two experimental studies that suggested that disordered coagulation was an important etiologic factor in producing acute lung injury in animals.[34,35] Other experimental studies, however, have found that coagulation factors and platelets are not important in the initial phase of increased lung vascular permeability.[36,37]

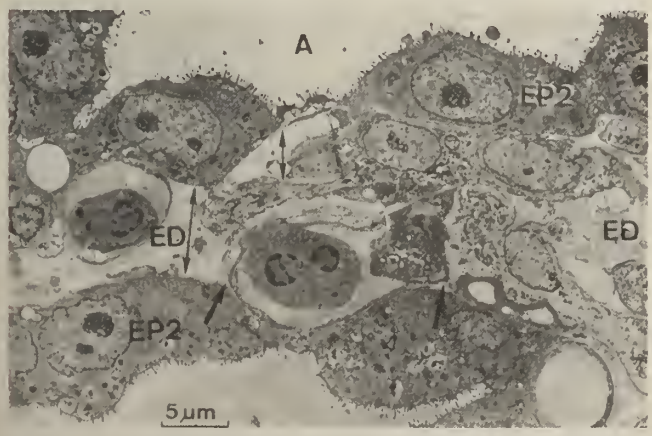

Figure 3.—An ultrastructural lung specimen from a patient about 1 week after nearly drowning shows the histologic features of the subacute stage of the adult respiratory distress syndrome. The septum is widened by interstitial edema **(ED)** fibers and cells **(double arrows)** and an almost continuous layer of bulky epithelial cells resembling type II cells **(EP2).** The single bold arrow refers to areas of fused endothelial and epithelial basement membrane. The patient had persistent sepsis from an abdominal source for 1 week (from Bachofen and Weibel[22]). A = alveolar space

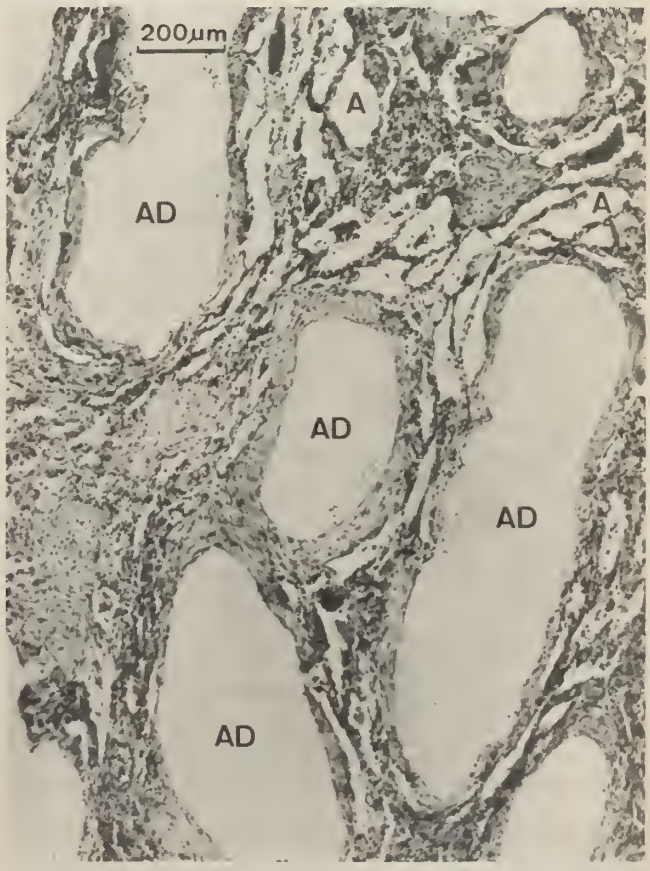

Figure 4.—Ultrastructural findings in a patient who died of progressive respiratory failure 2 weeks after abdominal septicemia began. Note there are compressed alveoli **(A)** and fibrotic tissue plates surrounding the air spaces **(AD)** (from Bachofen and Weibel[22]).

Evidence from studies in humans has implicated neutrophils in the cause of the initial lung damage in patients with ARDS. As described above, a large number of neutrophils collects in the lung in the early phase of acute lung injury.[21,38] Neutrophils also accumulate in the interstitium and air spaces of animals with experimentally induced acute lung injury.[39] Some investigators proposed that neutrophils could release toxic oxygen radicals or proteases that could then injure the endothelium and epithelial barriers in the lung.

Several experimental studies suggest that neutrophil depletion in experimental models attenuates the severity of acute lung injury.[37] In sheep given *E coli* endotoxin, the degree of lung injury was reduced if the neutrophils were first depleted with a chemotherapeutic agent like hydroxyurea. Subsequent studies have shown, however, that those studies may have been interpreted too narrowly, partly because chemotherapy affects cells other than neutrophils. The chemotherapy may have affected circulating monocytes and lymphocytes; thus, the effect may not have been related to neutrophils exclusively. In fact, one group of investigators at the University of Washington has shown that neutrophil depletion did not attenuate *E coli* endotoxin-induced lung injury in goats.[40] The role of neutrophils in the pathogenesis of ARDS remains unclear. Certainly lung injury and severe ARDS can occur without neutrophils.[41,42] The effects of neutrophils may of course also depend on injury to the endothelium that then enhances neutrophil-endothelial interactions.[43] The role of circulating monocytes both in injury and repair requires further investigation. Their role in releasing vasoactive cytokines and other factors that may amplify the inflammatory response remains to be established.

What about the resident lung cells themselves? Fifteen years ago we did not even know that intravascular macrophages existed in the lungs. Because of recent work from Warner, Brain, Staub, and other investigators, we now know that intravascular macrophages may be the first line of defense in the lung for endotoxemia or septicemia.[44,45] These cells seem to have the same properties of all macrophages. They release tumor necrosis factor in vitro, and they may be important in modulating the initial inflammatory response.

What about the damaging effects of mediators released by alveolar macrophages in the presence of acute lung injury? They may be a source of a large number of mediators that could injure the lung; however, their role has not been well established. It remains to be seen exactly whether they protect the lung or if they participate in the inflammatory response in a way that secondarily injures the lung.

What about the role of alveolar type II cells in the injury and repair after acute lung injury? I already mentioned the proliferation of type II cells in remodeling the epithelium after acute lung injury. Because alveolar epithelial type II cells are the source of surfactant, could injury to these cells contribute to the pathophysiology of ARDS? Obviously, ARDS is not as simple as the infant respiratory distress syndrome in that the latter is clearly initiated by a surfactant deficiency state. Nevertheless, one study showed that surfactant lavaged from patients with ARDS is abnormal biochemically, conceivably because of injury to type II alveolar epithelial cells.[46] Those findings do not prove that surfactant abnormalities play a major role in lung dysfunction, but they suggest that abnormalities in surfactant could play an important part in the poor lung compliance that occurs in ARDS. Finally, an area of interest to us is the possible role of type II alveolar epithelial cells in regulating alveolar liquid clearance and active ion transport. Type II alveolar epithelial cells have the capacity to transport sodium.[47,48] Studies in animals and in humans indicate that alveolar edema is cleared from the air spaces in the lung primarily by an active sodium transport system.[49,50] Type I epithelial cells may have this capacity, and type II alveolar epithelial cells certainly do. Furthermore, in studies in sheep and dogs, this ion transport system and rate of alveolar liquid clearance can be accelerated by β-adrenergic therapy.[51,52]

TABLE 5.—*Mechanisms for Injury and Repair in the Adult Respiratory Distress Syndrome*

Circulating cells	Possible mediators
Platelets	Complement system
Neutrophils	Prostaglandins
Monocytes	Oxygen radicals
? Lymphocytes	Proteases
Resident lung cells	Tumor necrosis factor
Intravascular macrophages	Other cytokines
Alveolar macrophages	
Epithelial cells, type II	
Fibroblasts	

Finally, of course, many mediators can amplify the inflammatory response (Table 5). Earlier I referred to the complement system. Although complement levels in the plasma do not predict lung injury in patients with sepsis, the role of complement in acute lung injury needs further clarification. In one recent experimental study, anti-C5a antibodies provided therapeutic benefit in a primate model of acute lung injury and the systemic manifestations of sepsis.[53] Products of both the lipoxygenase and the cyclooxygenase pathways may be involved in some of the acute responses. In a study done a few years ago, high levels of leukotriene D_4 were found in the edema fluid of ARDS patients.[54] There was a correlation between the elevated leukotriene D_4 levels and the degree of protein permeability. This finding may not indicate a cause and effect relationship but simply reflect the severity of lung injury. Oxygen radicals may be important in causing lung injury; some experimental studies have shown that agents that scavenge oxygen radicals reduce lung injury.[55] Proteases may be important in increasing the inflammatory response, but their net contribution to different types of lung injury remains to be established. Finally, the latest putative mediators include tumor necrosis factor and the interleukins. One recent experimental study indicated that the antibody to tumor necrosis factor attenuated the systemic and pulmonary effects of *E coli* sepsis in baboons if it was given two hours before the administration of live *E coli* organisms.[56]

Current and Future Therapy for ARDS

There are five categories to consider in the current and future therapy for ARDS:

- Early diagnosis, treatment, and the prevention of infection;
- Improve gas exchange;
- Limit the increased lung water;
- Increase the cardiac output and oxygen delivery because this is a systemic disease; and
- Decrease acute lung injury (Table 6).

TABLE 6.—*Current and Future Treatment of the Adult Respiratory Distress Syndrome*

Treatment Category	*Therapy*	
	Current	*Future*
Control infection	Prevention, early diagnosis, and treatment	Immunotherapy; aerosolized antibiotics
Improve gas exchange, reduce barotrauma	Positive end-expiratory pressure	Improved ventilatory modes; surfactant therapy
Limit or decrease pulmonary edema	Diuretics, maintain at lowest wedge pressure	β-Adrenergic agonists
Improve tissue oxygen delivery	Increase volume, vasopressors	Vasodilators
Attenuate pulmonary or systemic injury	Decrease Fio_2	Extracorporeal membrane oxygenation (venovenous bypass); oxygen radical scavengers; anti-tumor-necrosis-factor antibodies

Fio_2 = fraction of inspired oxygen

The first and foremost issue is the early diagnosis, treatment, and prevention of infection. We have already reviewed the importance of sepsis as a cause of ARDS and as a major factor in patients' ultimate outcomes. We obviously need to reduce nosocomial infections (hand washing, remove unnecessary catheters) and also to search for surgically treatable infections. If there is a positive blood culture and an unknown source, a surgical exploration of the abdomen is frequently helpful.[7] Some investigators have suggested that there should be a trial of prophylactic aerosolized antibiotics. This proposal is based on seven-day studies in baboons in which there was a decreased incidence of secondary pneumonia with aerosolized antibiotic therapy after acute lung injury was produced experimentally.[57] Perhaps the most promising new therapeutic option for preventing and treating infection is that of immunotherapy. In a landmark study published in 1986, surgical patients who were treated with serum that was harvested from patients immunized with the J5 antibody—which is basically an extract of the endotoxin glycolipid moiety common to most gram-negative organisms—showed a notable decrease in the incidence of shock and mortality in those patients who had gram-negative infection.[58] The controls were patients with gram-positive infections for whom the J5 antibody had no effect on outcome or the incidence of shock. This type of therapy is being tested in a number of medical centers, including our own, and it may provide an important new therapy for patients with ARDS or who are at risk for ARDS.

What about treatment to improve oxygenation and minimize additional lung injury? We know that the prophylactic use of 8 cm of water of PEEP does not prevent the development of ARDS.[59] There are no data that PEEP will help resolve pulmonary edema, though the issue is controversial.[60,61] PEEP is primarily supportive therapy for improving oxygenation and allowing the fraction of inspired oxygen to be lowered. None of the newer types of ventilation—pressure control, inverse ratio ventilation, or high-frequency ventilation—have been shown to have any favorable effect on the course of ARDS, although in some circumstances pressure support ventilation may be useful to reduce the work of breathing and optimize respiratory muscle function. The best hope in this category may be with the use of surfactant. This therapy may decrease lung compliance, reduce the mean airway pressure, and perhaps allow patients to be removed from a ventilator sooner. Human trials are currently underway.

What about treatment to decrease lung edema and still maintain an adequate cardiac output? It is reasonable to maintain a patient at the lowest possible pulmonary artery wedge pressure that does not interfere with an adequate cardiac output as defined by the pH and urine flow. There are no data that prove the value of actually dehydrating a patient. In fact, because most of the edema is in the air spaces, it is unlikely that lowering the left atrial pressure makes a major difference. The best hope for reducing lung edema might be to use β-adrenergic agonist therapy that could possibly accelerate the removal of the excess liquid from the air spaces to the interstitium where the lymphatics and circulation could disperse it.[51] Further studies are needed to test this possibility.

What about cardiac function and improving tissue oxygenation? I mentioned earlier that cardiac dysfunction is not uncommon.[15-17] First, however, hypovolemia should always be considered as the most likely cause of systemic hypotension. Hypovolemia develops because of the systemic and pulmonary capillary leak as well as the PEEP-induced reduction in venous return. Therefore, modest volume expansion is the first line of therapy. Preexisting heart disease, however, is not uncommon and may require treatment with vasopressors.[16,17] Coexistent clinical illnesses, such as sepsis, may also affect cardiac function. Drug overdoses with barbiturates may decrease cardiac output. Remember that there is considerable heterogeneity among patients with ARDS in terms of their cardiac function. There is some interest in trying to increase systemic oxygen delivery, possibly with the use of vasodilators, although the net effect of this type of therapy will have to be carefully assessed.

The use of various pharmacologic agents has been proposed for their possible value in attenuating systemic and pulmonary injury. Many have been tested experimentally, and a few have been tested clinically. The clinical studies show no benefit from any pharmacologic agents so far. In particular, the effects of treatment with corticosteroids have been tested in a prospective study by Luce and colleagues here at UCSF,[62] and they have shown that corticosteroids have no benefit in patients with ARDS; other investigators have shown no benefit of using corticosteroids in cases of sepsis.[63,64] In the future, oxygen radical scavengers, anti-C5a antibodies, or anti-tumor-necrosis-factor antibodies may be of some clinical value, although experimentally they provide benefits primarily when given before sepsis occurs. There are also some recent experimental data that a monoclonal antibody to the adherence-promoting leukocyte glycoprotein, CD18, can reduce systemic organ injury and improve survival after hemorrhagic shock.[65] Finally, there has been some renewed interest in extracorporeal membrane oxygenation on the basis of an uncontrolled Italian study.[66] A controlled prospective randomized study to examine the possible value of this approach is in progress at the University of Utah.

Table 6 summarizes current and possible future therapy for ARDS. Overall, the best hope for the treatment of pa-

tients with ARDS lies with the use of immunotherapy to prevent and treat infection, surfactant therapy to improve lung mechanics and gas exchange,[67] β-adrenergic therapy to accelerate the resolution of alveolar edema,[51] and possibly monoclonal antibody therapy for leukocytic adhering glycoproteins.[65]

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Epitomes

Important Advances in Clinical Medicine

General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in general and family practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Changing Role of Digoxin in Chronic Heart Failure

ALTHOUGH THE USE OF DIGOXIN to control supraventricular tachyarrhythmias is well established, its clinical efficacy in the long-term treatment of congestive heart failure in adults is less clear. Its effectiveness was recently reevaluated compared with placebo in a double-blind trial in patients with mild to moderate heart failure. Digoxin use was shown to increase the ejection fraction and decrease the number of hospital admissions related to heart failure but not substantially affect exercise tolerance or functional class. Digoxin appears to be most useful in patients with greater left ventricular dilatation, greater ejection fraction depression, a third heart sound, and more chronic and severe heart failure. Based on these findings, initiating digoxin therapy for heart failure in patients without atrial fibrillation, enlarged left ventricles, or a third heart sound should be carefully considered.

In patients with stable heart failure and sinus rhythm, the use of digoxin may not be necessary. Several recent studies have shown that digoxin therapy can be withdrawn with minimal adverse clinical or hemodynamic effects in 75% to 100% of patients in this category. The indications for treating patients who have been on long-term digoxin therapy should be reviewed periodically. The history and medical records should be carefully evaluated for definite evidence of previous heart failure. The presence of a third heart sound and a dilated left ventricle should be elicited on physical examination. In those patients in sinus rhythm whose cardiac status is stable and who have dubious indications for maintenance therapy, drug withdrawal should be considered with careful subsequent monitoring of their clinical state.

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Colposcopy in Human Papillomavirus Infection

IT IS LIKELY that most cervical cancer is a sexually transmitted disease caused by the human papillomavirus (HPV). The genital condyloma is the earliest expression of HPV infection. Condyloma must be considered to be the first expression of disease in the cascade of dysplasia—carcinoma in situ—or microinvasive or invasive cervical cancer.

We are in the midst of an epidemic of genital condyloma. It is critical that all family physicians be aware of the implications and diagnostic techniques required to evaluate their patients, both male and female, for the presence of lesions due to the human papillomavirus.

There are two groups of HPV associated with condyloma. The 6/11 group is usually associated with the classic, arboreal condyloma. Viruses in this group have polyploid mitoses, do not penetrate, and are not incorporated into the host genome. They are not associated with cervical malignancy, although one investigator has implicated them in vulvar malignancy. The etiologic agent of cervical malignancy is considered to be the 16/18 HPV group. Currently identified members of this group are types 16, 18, 31, 33, 35, and 42. These characteristically have aneuploid mitoses, penetrate, and are incorporated into the host genome. Cervical cancer specimens tested with DNA probes have shown the presence of 16/18 HPV virus types 95% of the time. The remaining 5% may represent 16/18 HPV subtypes for which no DNA probe is currently available.

The lesions associated with the presence of the 16/18 HPV are ubiquitous. They are flat and not easily identified by gross inspection. To discover the presence of lesions caused by these viruses, it is necessary to use a colposcope and counterstaining of the cervical, vaginal, vulvar, and possibly perianal or penile tissue with a 5% acetic acid (white vinegar) solution. The condylomatous lesions have an increased nu-

clear density and amount of keratin. Both the 6/11 and 16/18 groups appear white after vinegar is applied. Occasionally it is helpful to also stain the suspect tissue with Lugol's iodine solution. Iodine will stain areas containing glycogen brown and fail to stain areas devoid of glycogen. The latter are frequently condylomatous lesions.

Often more than one sexually transmitted disease is found in the same patient; therefore, a lesion that is classic for a 6/11 HPV may commonly be found associated with the presence of lesions caused by the 16/18 HPV.

Colposcopy is indicated in the evaluation of all patients with class II findings on Papanicolaou smears that have persisted three or more months and all patients with class III or higher findings. A pathologist's notation of the presence of "koilocytes," a cell classic for the presence of HPV, is also an indication for a patient to be examined colposcopically, as is the presence of a condyloma. As with all sexually transmitted diseases, sexual partners should be advised to seek examination and treatment if one is found to have condylomata. Colposcopy is an easily learned technique that can be incorporated into primary care practice.

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Preventing and Treating Acute Mountain Sickness

ACUTE MOUNTAIN SICKNESS (AMS) is a syndrome characterized by headache, nausea, vomiting, insomnia, and lassitude. The syndrome, part of a continuum including high-altitude pulmonary edema and high-altitude cerebral edema, generally occurs three to eight hours after lowlanders ascend to altitudes greater than 3,000 m (9,800 ft). Because of increased recreational time and improved transportation systems, it is now common for physicians in mountainous areas to see the consequences of altitude illness. The incidence varies with the rate of ascent and the altitude attained. More than 60% of climbers on Mount Rainier (Washington) suffer at least mild AMS. While only 12% of Colorado skiers experience symptoms, AMS causes an estimated annual loss of revenue by the tourist industry of the mountain states of $50 to $75 million.

To reduce the incidence and severity of AMS, a graded, staged ascent and a high-carbohydrate diet are recommended. Chemoprophylaxis can also be recommended in certain circumstances where a graded ascent is not possible. The prophylactic use of acetazolamide is usually effective. Possible mechanisms include increased ventilation, metabolic acidosis, improved sleep, the inhibition of cerebrospinal fluid production, diuresis, or a combination of the above. The drug therapy is usually started 12 to 24 hours before ascent and continued for 24 to 48 hours at altitude. Adverse effects include peripheral paresthesias, polyuria, dysgeusia for carbonated beverages, myopia, nausea, and vomiting. Because some of the side effects resemble AMS, some physicians advise trials of the drug at a low elevation before the patient goes to altitude.

Recent studies suggest that the use of dexamethasone is more effective than that of acetazolamide as prophylaxis for AMS symptoms. The mechanism is unknown but probably involves reducing cerebral edema, although antiemetic effects and steroid euphoriant effects may also play a role. Dexamethasone given in a dosage of 12 to 16 mg daily (lower doses are inadequate) starting two to four hours before ascent is recommended. Stopping the therapy before acclimatization takes place may result in rebound altitude illness. The use of dexamethasone for AMS prophylaxis is not without its risks and should be limited to special circumstances because of inadequate experience, the severity of possible side effects including acute psychosis and drug withdrawal, and the benign nature of AMS in most cases. Current recommendations generally limit the use of dexamethasone for AMS prophylaxis to persons making forced, rapid ascents to high altitude for a short stay and with a guaranteed retreat route, thereby avoiding the risk of drug withdrawal.

The treatment of choice for all forms of high-altitude illness is descent. Mild forms of the illness, however, may not mandate descent, or descent may be impractical, and the clinician may wish to try other methods. Mild AMS can be treated by waiting for further acclimatization at the same altitude. Administering analgesics, prochlorperazine, or acetazolamide may provide symptomatic relief. If the symptoms progress, descent is mandatory. For moderate to severe AMS (early cerebral edema), descent should be attempted if possible. The administration of dexamethasone, 4 mg every six hours, is probably indicated. A prompt response (four to eight hours) is expected. This drug therapy must be continued for 48 hours, then tapered or continued until the victim has descended or acclimatized.

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Evaluating Palpable Breast Lumps With Negative Mammography

BREAST CANCER is an increasingly important problem in health care. Much is written about screening and diagnostic measures. It is important to realize that when a breast lump is present, a normal mammogram does not preclude the need for biopsy to establish the diagnosis.

It has been well established that mammography is important in screening for breast cancer. Authorities generally agree that mammography is more accurate than palpation at finding minimal breast lesions. This was borne out in studies at breast cancer detection centers in Milwaukee and Cincinnati. In its present state of development, however, mammography will yield a certain percentage of falsely normal results (false-negatives). There are several reasons for this: subtle or absent signs in some lesions (in situ and intraductal lesions may show no obvious radiographic patterns), difficult-to-

detect locations such as near the chest wall or in the tail of the breast, and inaccurate reading. The likelihood of a false-negative mammogram is increased in patients with small breasts, dense breasts, and with retroareolar lesions. Using Wolfe's classification, the likelihood of a cancer being missed in a fatty (N_1) breast is only 2.08% but rises to 56.25% in a very dense (P_2) breast.

Thus when there is a suggestive, palpable breast lump, the patient cannot be safely followed by observation, repeated palpation examinations, and periodic mammograms. In such a patient, a definitive diagnosis must be established by examining a tissue specimen. The tissue specimen can be obtained by excisional biopsy and pathologic diagnosis, or, in selected circumstances, cells obtained by thin-needle aspiration for cytologic diagnosis. Only then will the risk of a normal mammogram giving a false sense of security be avoided.

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Asymptomatic Bacteriuria During Pregnancy

SIGNIFICANT BACTERIURIA in asymptomatic pregnant women was defined by Kass in 1960 as greater than 10^5 organisms per milliliter of clean-voided urine. The prevalence of asymptomatic bacteriuria during pregnancy is 2% to 14%. Factors associated with a higher risk include advanced age, higher parity, and a lower socioeconomic status. In approximately 20% to 40% of untreated women with asymptomatic bacteriuria, a symptomatic urinary tract infection, such as cystitis or pyelonephritis, will subsequently develop during the course of pregnancy or immediately postpartum. Conversely, acute pyelonephritis will develop in less than 5% of patients with asymptomatic bacteriuria who have been appropriately treated with antibiotics.

The basic factor predisposing to urinary tract infection during the prenatal period is the relative stasis of urine caused by pregnancy-induced changes. Hydroureter is common during the last half of pregnancy. Progesterone causes the ureters to dilate, while the enlarging uterus leads to mechanical compression. In addition, changes in a pregnant woman's immune system may make her more susceptible to infection.

Escherichia coli accounts for about 80% of the identified pathogens. *Klebsiella pneumoniae, Proteus mirabilis,* and *Enterobacter* organisms are also common infecting organisms.

Several investigators have found an increased incidence of premature delivery in untreated patients with asymptomatic bacteriuria. Patients who are treated and remain unaffected, however, do not appear to be at increased risk for preterm delivery. The patients at highest risk are those in whom acute pyelonephritis develops, with associated premature labor and advanced cervical dilation.

While urine culture is considered the gold standard for diagnosing urinary tract infections, other methods have been proposed as cost-effective means for screening obstetric patients for asymptomatic bacteriuria. Routine urine analysis, Gram's stain, and chemical analysis to test for leukocyte esterase and nitrite have not been proved sufficiently sensitive. The dip-slide (Uricult) test has been valuable in the ambulatory setting. If there is growth on the MacConkey agar side of the paddle (specific for the growth of gram-negative bacilli) at a colony count of 10^4 or more, a positive traditional culture can be expected 81% of the time. This is the predictive value of the positive result. It is judicious to then also do routine culture and sensitivity testing. If there is growth on the cysteine-lactose-electrolyte-deficient agar side of the paddle (which supports the growth of all organisms) at a colony count of 10^5 or more, culture before treatment is necessary because of the high percentage of false-positives. Recently a test known as the FiltraCheck-UTI bacteriuria detection system has been evaluated. This makes use of a growth-independent colorimetric method that uses stable reagents and a disposable filter disk. It is inexpensive and can be done in one minute. Initial results have shown a sensitivity of 96.5% and a specificity of 79.7%. It may be useful in the future as an initial screen for asymptomatic bacteriuria.

Because the most commonly identified organism is *E coli,* current treatment recommendations include administering an antimicrobial drug for 7 to 14 days, such as ampicillin, nitrofurantoin, sulfonamides (except in the third trimester), or first-generation cephalosporins. The efficacy of single-dose therapy for asymptomatic bacteriuria during pregnancy has been confirmed, with the eradication of bacteria in 70% to 80% of cases. Recurrence rates are less than 5%. The advantages of single-dose therapy include greater patient compliance, lower cost, fewer side effects, and less potential hazard to the fetus. This regimen is most appropriately used in women for whom the above factors are significant and who have not had urologic problems. A culture should be repeated at the completion of therapy, and patients with a positive result need to be re-treated. It has been recommended that patients treated for acute pyelonephritis be placed on suppressive antibiotic therapy or have regular repeat cultures for the duration of their pregnancy.

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Lyme Disease

FIRST DESCRIBED in November 1975, Lyme disease has become the most common tick-borne disease in the United States. The disease is transmitted by the bite of a tick, *Ixodes dammini,* although only a few patients will recall the tick bite. In 1984 the causative organism of Lyme disease was identified to be a *Borrelia burgdorferi.*

Lyme disease indiscriminately affects both sexes and all age groups of patients and most often occurs between June and September. The disease occurs predominantly in three regions in the US—the coastal Northwest; Minnesota and Wisconsin; and parts of California, Oregon, Utah, and Nevada.

Lyme disease occurs in three distinct clinical stages. Stage I is characterized by a rash, erythema chronicum migrans, which develops 2 to 30 days after inoculation by the tick bite. This rash occurs in 60% of patients and is often accompanied by profound fatigue, low-grade fever, chills, stiff neck, arthralgias, and myalgias. The second stage of disease occurs in only 15% of patients and includes neurologic and cardiac symptoms. Stage III occurs weeks to years after the initial infection and consists of polyarthritis that is clinically similar to rheumatoid arthritis. This arthritis will develop in about 60% of patients who have not received appropriate treatment of stage I or II.

The treatment of choice for Lyme disease is to administer tetracycline, 250 mg four times a day for ten days. Children younger than 8 years may be given penicillin, 50 mg per kg body weight per day, or erythromycin, 30 mg per kg per day for ten days. The symptoms may worsen immediately following the initiation of antibiotic therapy, indicating the Jarisch-Herxheimer reaction. Early recognition and treatment can substantially reduce the incidence and severity of the arthritis associated with stage III disease.

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Prenatal Evaluation for Hepatitis B Surface Antigen

EACH YEAR 3,500 newborns become hepatitis B virus carriers following the perinatal transmission of hepatitis B virus infection. Hepatitis B is easily transmitted during pregnancy, and most infected newborns (85% to 90%) will become long-term carriers.

At-risk newborns treated early have an 85% to 95% reduction in the carrier rate. Unfortunately, risk factor screening identifies only 35% to 65% of hepatitis B virus carriers, and risk factors are not consistently applied in practice. In response to these difficulties and in light of the substantial morbidity of hepatitis B in newborns, the Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control now recommends that all prenatal patients be screened for hepatitis B virus infectivity.

The ACIP recommends that testing for the hepatitis B surface antigen be added to the laboratory tests done on the first prenatal visit. Women testing negative should be rescreened if involved in high-risk behaviors during pregnancy, such as intravenous drug use. Women testing positive should be considered carriers and their newborns treated.

Once the hepatitis B surface antigen is identified in a patient, the following actions should occur:

- If there is evidence of acute or chronic liver disease, additional therapy may be indicated for the woman.
- Household contacts and sexual contacts need to be screened, and, if susceptible, prophylactic treatment (hepatitis B vaccine) needs to be instituted.
- The newborn infant will need to be treated as follows: hepatitis B immune globulin, 0.5 ml, is given intramuscularly when the infant is stable (within 12 hours, if at all possible); hepatitis B vaccine, 0.5 ml, is given intramuscularly at a separate site at the same time as the hepatitis B immune globulin, and repeat doses are given at 1 and 6 months of age; the child should have hepatitis B surface antigen and antibody testing at 12 to 15 months of age to assure effectiveness of the treatment.

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Preventing Teenaged Addiction to Tobacco

TOBACCO ABUSE is the most important preventable cause of illness and death in our society. The highly addictive nature of tobacco was well documented by the most recent Surgeon General's report. Cessation programs are certainly worthwhile but have shown limited success in treating addiction. The primary prevention of tobacco abuse therefore seems to hold greater promise for controlling the tobacco pandemic.

Few people begin to smoke after reaching adulthood. In fact, 60% of all smokers start using tobacco by the age of 14 years, and 90% start by the age of 19. It is therefore logical to direct preventive efforts at children and adolescents.

Each year our children are bombarded with $2 billion worth of advertising that attempts to associate tobacco use with "coolness," sexiness, athletics, and the attainment of adulthood. In a highly successful effort to make chewing tobacco more attractive to children, one company markets little teabaglike packets of candy-flavored snuff. Once addicted, teenaged boys are likely to become lifelong consumers of tobacco products.

These Madison Avenue techniques cannot be effectively countered with scare tactics—a 14-year-old boy is seldom impressed by the fact that his smoking now may cause lung cancer when he is 60. On the other hand, humor and parodies of tobacco ads are apparently more effective in countering the promotion of tobacco. The goal is to "laugh the pushers out of town," while explaining the harmful effects of tobacco in terms to which children can relate: "Smoking gives you yellow teeth and bad breath and makes you *less* attractive to the opposite sex." "Smoking doesn't make you 'cool'—only 'nerds' smoke cigarettes or dip snuff." "Tobacco is a 'rip-off,' and money that kids waste on tobacco could be spent on clothes and records instead."

Physicians can cooperate with local school districts to develop tobacco education curricula for fifth- to seventh-grade students. A model program is available from DOC (Doctors Ought to Care, 1423 Harper St, Augusta, GA 30912), with lesson plans for several teacher-conducted sessions, followed by a slide presentation by a physician. The program culminates in a poster contest, with the winning student's poster displayed as a billboard in a prominent location in the community.

Tobacco companies spend millions of dollars to sponsor sporting events, circumventing the regulations that prohibit the explicit advertising of tobacco products on television. Through the sponsorship of sports, they attempt to establish an association between tobacco and athletic prowess and to buy an aura of respectability. Although the industry denies it,

much of this sports-related tobacco advertising appears to be directed at youth. Some communities have responded with parodies such as the "Emphysema Slims Tennis Tournament" and the "Dead Man Chew Softball Tournament." Others have used paid counteradvertising on television, radio, billboards, and bus benches to tell the truth about tobacco and to point out the insidious techniques used in its promotion.

These new approaches for preventing tobacco abuse by children have been pioneered by DOC. The American Medical Association, the American Academy of Family Physicians, and the American Cancer Society are all beginning to adopt these new methods, while continuing their efforts to encourage smoking cessation.

Through counteradvertising and tobacco education programs on the local and national levels, it may be possible to reduce the number of new smokers and thereby decrease the impact of the tobacco-related diseases that presently kill 1,000 Americans every day.

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Tobacco and Youth Reporter, STAT (Stop Teenage Addiction to Tobacco), PO Box 50039, Palo Alto, CA 94303

Diarrhea in Children

FOR MANY CLINICIANS, the treatment of diarrhea is straightforward: the patient is not given anything orally while the intravenous (IV) administration of fluids is started, then the patient is given clear liquids for 24 to 48 hours, followed by a BRAT—bananas, rice, applesauce, toast—diet. Recent studies, primarily in third-world populations, have shown that this is not the optimal therapy.

Perhaps the biggest change has been in IV fluids therapy, which is now recognized as rarely necessary. Instead, oral rehydration solutions—World Health Organization Oral Rehydration Solution (WHO ORS), Pedialyte, Lytren—are available and effective in replacing lost fluids. It should be emphasized that many "clear liquids" such as soft drinks and popsicles are not ideal therapies: they are low in sodium and potassium, key electrolytes in this disease state, and high in carbohydrates, a fact that may prolong the diarrhea. If soft drinks or fruit juices are used, they should be diluted one part beverage to two parts water because they are hyperosmolar and may draw water into the lumen. In addition, commercially prepared soup (high in salt content) and tap water (no electrolytes) should not be a major component of the therapy. For these reasons, many clear liquids should be avoided, except in limited quantities or in mild cases.

Because continued breast-feeding is beneficial, there is a growing thought that the disease state responds better to the additional nutrition than to starvation. In underdeveloped countries where no IV fluids are available and the WHO ORS formula is widely used, research has shown that replacing the glucose in the oral rehydration solution with rice powder or protein actually decreases the recovery time. Recent studies in England and the United States have confirmed these findings. Thus, the trend is now to give oral clear liquids (as described above) in the first few hours of illness followed by early feeding of a carbohydrate-protein-electrolyte mixture while the patient still has diarrhea. This regimen is thought to be not only safe but preferred because it decreases morbidity and costs.

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Circumcision Reevaluated

DESPITE BEING THE MOST COMMON surgical procedure in the country, circumcision has been the center of tremendous and often intense debate for the past 40 years. So adamant have the two camps been that little consensus has been achieved. Thus, though the American Academy of Pediatrics is reevaluating its 18-year-old anticircumcision stance, it is unlikely the controversy will be resolved. Though there are currently no answers, family physicians should be updated on the debate in order to better inform parents and to assist in the needed research.

Central to the debate is the evaluation of health risks and benefits. Most health risks of remaining uncircumcised—balanitis, posthitis, penile cancer, phimosis, and foreskin trauma—are too insubstantial in frequency or morbidity to play a role in decision making. The recently discovered tenfold increase in urinary tract infections in uncircumcised persons has swayed many to favor the procedure, but the long-term effects of this increased risk are not known. In addition, the original belief that the procedure is "harmless" in most infants has come into question with the recent realization that neonates do feel pain and show pronounced physiologic and biochemical changes to this pain.

What role, then, does the family physician have? It is clear there is no consensus, and the field is evolving. To strongly adhere to one belief or the other is probably unwise. Until such time that the several questions regarding circumcision and the uncircumcised state are answered, supportive counseling of parents is the best plan.

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The Melanoma Epidemic

ALTHOUGH THE EPIDEMIC of disease mediated by the human immunodeficiency virus has rightfully taken much of our attention, primary care physicians must not forget that we are also in the midst of an epidemic of malignant melanoma. The incidence of malignant melanoma roughly tripled between 1950 and 1970 and has increased by 700% over the past 55 years. It is estimated that by the turn of the century malignant melanoma might well afflict 1% of the general American population.

It is extremely important that primary care physicians be trained to diagnose malignant melanoma in its early stages because prognosis is best correlated with the thickness of the lesion. The relationship of melanoma thickness to five-year survival is as follows: 0 to 0.85 mm, 99%; 0.86 to 1.69 mm, 94%; 1.70 to 3.59 mm, 81%; and 3.60 mm or larger, 49%.

Definite risk factors for melanoma include white race, particularly those of Celtic heritage; sun exposure, particularly with episodes of sunburn; dysplastic nevi, particularly familial dysplastic nevi; and large congenital nevi (greater than 20 cm).

Patients should be encouraged to report any change in a skin lesion, particularly recent growth, bleeding, pain, or the development of a new lesion. Physicians should remove or take a biopsy of any skin lesion that is at all suggestive of melanoma.

Physicians should be vigilant in screening for melanoma and should keep in mind the rule of "ABCD": *A*symmetry, *B*order irregularity, *C*olor variegation, and *D*iameter generally greater than 6 mm. Various textbooks and monographs are available to assist physicians in recognizing melanoma in its earliest stages.

The familial dysplastic nevus syndrome is an autosomal dominant condition with a lifetime incidence of melanoma approaching 100%. Dysplastic nevi tend to be more plentiful (25 to 75 per person) and larger (6 to 15 mm) than common nevi. Dysplastic nevi are acquired after birth and often have irregular borders, variegated colors (particularly tan, brown, and pink), and indistinct borders fading into the adjacent normal skin.

Primary prevention includes avoiding sunlight, using protective clothing and hats, and using sunscreens as early as infancy and throughout adult life. Sunbathing and the use of tanning parlors should be actively discouraged. The melanoma epidemic is presenting all primary care physicians with the challenge of the primary prevention of the disease and the early detection of melanoma at a time when it is completely curable.

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Silent Myocardial Ischemia

ALTHOUGH MYOCARDIAL ISCHEMIA AND INFARCTION are major health problems in the western world, our understanding of this disease remains incomplete. Physicians think of ischemic heart disease as a clinical syndrome manifested by chest pain or other "anginal equivalents." The cardiologic literature over the past decade has clearly shown, however, that silent myocardial ischemia is a common manifestation of coronary artery disease. In fact, there is every reason to think that silent myocardial ischemia carries the same (or worse) clinical significance as symptomatic coronary artery disease. This should come as no surprise because one of five sudden death victims in the United States has no history of heart disease, yet commonly has evidence of advanced arteriosclerotic disease in the coronary arteries at autopsy.

Silent myocardial ischemia has been studied predominantly using two tools: ambulatory Holter electrocardiographic monitoring and the exercise test. Although factors that make myocardial ischemia painless in some persons are not completely understood, it is a common phenomenon. In a study of patients with angina with known coronary artery disease documented by arteriography, 75% of all ambulatory episodes of ischemia were painless. Silent myocardial ischemia shares the same circadian variations as angina pectoris and myocardial infarction, occurring most often in the morning, generally between 0600 and 1200. Silent myocardial ischemia, however, seems to develop more commonly at rest and at lower levels of heart rate and blood pressure. This suggests, but does not prove, that silent myocardial ischemia may be due to enhanced coronary artery vasoconstriction, as opposed to an increase in myocardial oxygen demand.

Although it is becoming clear that the problem of silent myocardial ischemia is one of major proportions, the solution is less clear. Cohn recommends screening exercise tests in all patients with two or more major risk factors for coronary artery disease, particularly those with diabetes mellitus because of visceral neuropathy. Patients with abnormal results on treadmill tests, but ST depression less than 2 mm in stage I or II of the Bruce protocol, should have radionuclide imaging. The decision to proceed to coronary arteriography depends on the patient. In general, patients suffering a myocardial infarction undergo exercise testing, usually at least two to three weeks after the infarction. Silent myocardial ischemia in patients with stable angina pectoris is often best detected by ambulatory Holter monitoring.

Currently there is no reason to treat silent myocardial ischemia any differently than symptomatic angina pectoris. Risk factors should be modified to the extent possible. The decision to proceed to arteriography and ultimately angioplasty or coronary artery bypass grafting must be tailored to each patient. In patients who have suffered a myocardial infarction and subsequently show silent myocardial ischemia, many data suggest a long-term benefit with β-blocker therapy. Patients with angina pectoris and silent myocardial ischemia are subject to vasospasm and therefore may benefit from using calcium channel blockers, as well as nitrates and β-blockers.

In the forthcoming years, much new information will surface regarding silent myocardial ischemia. Because of the extent of this public health problem, primary care physicians should make every effort to keep abreast of new developments in the diagnosis and treatment of the disorder.

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Cohn PF, Kannel WB: Recognition, pathogenesis, and management options in silent coronary artery disease: Introduction. Circulation 1987; 75 (pt 2):III

Fluoroquinolones

THE FLUOROQUINOLONES are a remarkable new group of bactericidal antibiotics related to nalidixic acid. Among other effects, they appear to act on DNA gyrase, an enzyme involved in DNA replication. The agents currently available in the United States include norfloxacin and ciprofloxacin. Because these agents show a wide spectrum of bactericidal activity and an apparently excellent safety profile, they can be extremely effective agents in a primary care practice but must be used wisely.

The spectrum of antibacterial activity of these agents includes *Escherichia coli, Klebsiella, Hemophilus influenzae* (including ampicillin-resistant strains), meningococci, *Branhamella catarrhalis, Salmonella, Shigella, Campylobacter jejuni, Aeromonas, Yersinia enterocolitica,* staphylococci (including methicillin-resistant *Staphylococcus aureus*), and *Pseudomonas aeruginosa.*

Norfloxacin and ciprofloxacin have been shown to be effective for the treatment of genitourinary and gastrointes-

tinal tract infections, uncomplicated gonorrhea, prostatitis, and as prophylactic agents against travelers' diarrhea and gram-negative infections in patients with neutropenia. The fluoroquinolones should not be used to treat anaerobic infections, and their usefulness in a variety of other situations, particularly infections of the central nervous system, is unknown.

Adverse effects of the fluoroquinolones have been predominantly mild—nausea, vomiting, abdominal pain, dizziness—but neutropenia and elevated serum aminotransferase levels have been reported. Rare episodes of seizures and reversible arthropathy have been reported with these agents. The use of fluoroquinolones is not recommended for patients younger than 17 years or pregnant or breast-feeding women.

Primary care physicians should resist the temptation to use the fluoroquinolones as "shotgun" therapy for various outpatient infections. Where possible, particularly in uncomplicated genitourinary tract infections, older and cheaper agents, such as the sulfonamides and penicillins, should be used. Because the development of bacterial resistance to an antibiotic is directly proportional to its use, the fluoroquinolones should be reserved for cases in which they clearly show superiority to conventional agents. Also, primary care physicians must be vigilant of the possibilities of serious adverse effects, particularly central nervous system toxicity and arthropathy.

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Posttraumatic Stress Disorder in Southeast Asian Refugees

SINCE 1975 MORE THAN 700,000 REFUGEES from Southeast Asia have immigrated to the United States. The largest number of these have settled in California. Initial health care focused on infectious disease considerations of hepatitis, parasitology, and diseases endemic in the third world. Further evaluation revealed a substantial difference between the better educated, more highly skilled refugees in the first wave of immigration in 1975 to 1978 and the second wave of war refugees in 1978 to 1979. In the past five years, researchers at several mental health clinics focusing on refugee psychiatric problems have begun to record the previously undetected extent of significant psychological problems in this population. Mollica and co-workers in Boston, Westermeyer in Minnesota, and Kinzie and Fleck in Portland, Oregon, in particular, have reported the extent and severity of depression and posttraumatic stress disorder in Southeast Asian refugees, particularly those in the second wave of immigration. They have also reported that the Cambodian refugees who suffered some of the atrocities of the Pol Pot regime appeared to be the most severely affected.

These researchers have been working primarily in mental health centers designed for refugee health care. They all comment, however, on the consistent pattern of somatization in Southeast Asian refugees and the cultural inhibition in identifying mental health problems. Therefore, refugees are more likely to present to primary care physicians than to mental health services. Unless family physicians and internists are alert to the symptoms of posttraumatic stress disorder, the diagnosis may be missed. The symptom complex of the disorder includes flashbacks, nightmares, severe difficulty concentrating, panic attacks, strong startle responses, emotional blunting, and extreme avoidance of stimuli that induce memories of the traumatic experiences. The somatic presenting complaints are frequently headaches, dizziness, and abdominal, back, or joint pain.

With more culturally aware assessments, primary care physicians can play a key role in determining the prevalence of this problem, in mobilizing appropriate consultation and community resources, and in minimizing the iatrogenic risks of multidrug therapy and unnecessary diagnostic evaluations. They may also be better able to establish supportive continuing relationships with these patients, who tend to drift from physician to physician seeking relief for their various somatic complaints. Only with continuity will it be possible to help Southeast Asian refugees begin to understand and grapple with this complex disorder.

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Editorials

Integrity in Medicine

It has generally been assumed by physicians and the public that ours is an honest profession whose integrity has been unquestioned. There is now disturbing reason to believe that this assumption is no longer correct, if indeed it ever was. There have been what to this physician are shocking examples of dishonesty, plagiarism, and outright fabrication of results at some of the most prestigious research institutions in the nation. Robert Petersdorf, president of the Association of American Medical Colleges, is reported to have described to a large audience at a recent meeting of that organization what he termed academic "irregularities" among premedical students seeking admission to medical school and among medical students who are in school. In a total of 952 cases of fraudulent transcripts, unauthentic letters of recommendation, inaccurate and incomplete credentials, and irregular test behavior were found. He went on to express concerns about cheating among students who were already in medical school and then to wonder about the relationships, if any, between this behavior and their subsequent performance in academic research or practice. In any case, it is sad but true that there are physicians in practice who have been found to be dishonest in their billings to third parties for care they may or may not have actually rendered.

All of this is difficult to deal with at any level. It probably has always existed, but, for better or worse, the medical profession is now in the goldfish bowl of public scrutiny. It would be useful to try to do something to counteract this apparent erosion of integrity among physicians. One is reminded of the "ethical physician" campaign in the last century to counteract quackery. Ethical physicians were adequately trained and did not practice quackery, and this was publicized. Physicians who belonged to medical societies were identified as ethical physicians. Ethical is not the right word for today. But perhaps some way could be found to make professional integrity a sine qua non for membership in organized medicine. Something like this could be a powerful counterforce to those who would cheat and corrupt this noble profession.

MSMW

Malignant Pericardial Effusions

The timely and effective management of complications of malignancy consumes the majority of oncologists' time and is more taxing of specialists' clinical skills than are the selection and administration of a well-researched drug regimen for inducing a complete or partial remission. Nevertheless, the medical literature devotes far fewer pages to new insights concerning complications, their diagnosis, and management than to innovative treatment regimens designed to arrest or retard tumor growth. Thus, the review by Buzaid and colleagues in this issue of the journal is a welcome addition to our literature as it summarizes studies addressing the current knowledge of an important complication in neoplasia, that of malignant pericardial effusions. The article is balanced, discusses the clinical setting in which malignant effusions occur, and reviews approaches to the diagnosis and treatment of this potentially life-threatening disorder.

For primary care practitioners who frequently assume responsibility for cancer patients, it is relevant to underscore the fact that malignant pericardial effusions are not rare events. Although almost any neoplasia may be associated with symptomatic pericardial disease, patients with carcinoma of the lung and breast, malignant lymphomas, leukemias, and melanomas are particularly prone to the development of effusions. The authors suggest that as many as 40% of patients with malignancy and pericardial disease have benign disorders of the pericardium. This seldom creates a problem in the differential diagnosis since restrictive pericardial disease with effusion is most commonly associated with radiation therapy to the chest and pericardium, and idiopathic pericarditis is usually associated with a friction rub, chest pain, dyspnea, and fever. This constellation of findings is typical of idiopathic pericarditis and helps to separate it from malignant pericardial effusions, which frequently lack a rub, pain, or fever. The most common symptoms of malignant pericardial effusions are those of dyspnea and cough, which can confuse a clinician, who may attribute these symptoms to the further spread of malignant disease in the lung parenchyma. Since these symptoms can be quite debilitating and, in fact, lead to death when associated with cardiac tamponade, it is important to consider the diagnosis of malignant pericardial effusion in this clinical setting because, once diagnosed, it is easily treated. Although survival may not be extended, the quality of life can be immeasurably improved following successful intervention.

Buzaid and co-workers consider the various therapeutic interventions, discussing their risks and outcome, and coming down on the side of surgical intervention whenever the clinical situation permits. The surgical approach is attractive, for it is brief and effective, albeit from a patient's point of view it may be less desirable than pericardial sclerosis. The cost of the surgical approach surely must exceed that of pericardial sclerosis; furthermore, the discomfort to patients is apt to be greater following the surgical attack than following medical management. Were efficacy clearly better employing the surgical approach, one could easily side with the authors. Nevertheless, since such data are not provided, it is reasonable to agree with the editors of *The Medical Letter,* who give the nod to pericardial sclerosis in such situations.[1] Be that as it may, as the authors point out, if one's colleagues in surgery are particularly skilled using the surgical approach and one lacks the cardiologic backup support, there may be other reasons to select one technique over the other since both have comparable outcomes.

From the surgical standpoint, it seems reasonable to do as little as possible to solve the problem, and here the small window seems to be preferable to the more extensive approach, including perhaps stripping and a general anesthetic. With life being so short and the likelihood of recurrent effusions being small following either the medical or surgical approach, the goal should be to keep the morbidity to its lowest and the patient functioning as long as possible.

It is not likely that more effective treatment strategies will be developed for malignant pericardial effusions in those patients with refractory tumors; the success rate for both the surgical and medical management currently approaches 100%. It is of some interest, though, that the dose of tetracycline recommended for ablating the pleural space[2] is essen-

tially the same as that for ablating the pericardial space, as reviewed by Buzaid and associates. Since the surfaces of the pericardial sac are many times smaller than those of the pleural space, one wonders whether or not too high a dose of tetracycline may be being proposed for ablating the pericardial space. To this point, it is interesting that Shepherd and colleagues recommend 500 mg of tetracycline in 20 ml of a saline solution rather than the 1-gram dose and base their conclusions on the fact that efficacy seems comparable but pain is increased in patients who receive 1 gram of tetracycline.[3] When our pharmacy tested the pH of 1 gram of tetracycline in 20 ml of a saline solution and compared it with that of 500 mg of tetracycline in 20 ml of a saline solution, it was found that the pH for both ranged between 2.5 and 3, which is the range that is thought to be required to induce pericardial sclerosis. Perhaps, therefore, the 500-mg dose is the preferred regimen for pericardial sclerosis.

The management of any chronic disease is a challenge to our profession. Buzaid and colleagues focus our attention on a rather common oncologic problem that frequently goes undiagnosed, particularly when not considered. In the process of reviewing this topic, they have given us some specific guidelines for management. Whether one agrees with me that the medical approach may be the better, or sides with the authors who suggest that the surgical approach is preferred, the real thrust of their article must be kept in focus. It challenges us to be aware of the potential of the problem and to plan immediate interventions to resolve this life-threatening complication.

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Lightning May Strike Twice

THE IDEA TAKES some getting used to at first. Patients with cancer may get into trouble once again, as the clinicopathologic conference in this issue of the JOURNAL so vividly illustrates. Only this time, the problem is not the initially treated tumor, a low-grade astrocytoma here, but a second, more malignant tumor, an osteogenic sarcoma, which arose as a direct result of radiation therapy. What are the risks? In which patients will it develop? What are the radiation doses? How long does it take for a second tumor to manifest itself? and, finally, What happens to the patients? These are some of the pertinent questions one should balance against the curative effects of irradiation on the primary cancer and the prolonged disease-free interval provided by the latent period.

Sarcomas secondary to irradiation constitute a rare albeit serious late effect of radiation therapy, but it is difficult to obtain a quantitative estimation of the risk. Unfortunately, only scattered reliable appraisals are available, but some reasonable calculations are on hand as more than 500 patients with postradiation sarcomas have been reported so far. Among more than 1,200 histologically verified osteogenic sarcomas of bones and soft tissues diagnosed and treated at Memorial Sloan-Kettering Cancer Center, 66 (5.5%) arose as a direct consequence of either external or internal ionizing irradiation.[1] Kim and associates from the same medical center estimate an incidence of 1.3% eight years after chemotherapy and irradiation for Hodgkin's disease.[2] The series reported, however, is small and the follow-up time brief. Mays and co-workers reported a long-term survey of 899 German patients, many of them children, who were treated for tuberculosis and ankylosing spondylitis by repeated injections of the short-lived radium isotope Ra 224: a bone cancer eventually developed in 53 (6%) of the patients.[3] This probably represents the uppermost limit of the estimate since the follow-up time is now at least 30 years.

The most recent large-scale, multi-institutional epidemiologic survey by Tucker and colleagues, which covers more than 9,000 patients treated for childhood cancer by irradiation, provides similar risk projections.[4] This study computes the cumulative mean probability of inducing a malignant bone tumor by therapeutic irradiation at 20 years after therapy to be $5.5\% \pm 2.1\%$. The absolute risk is calculated to be $9.4 \times 10^{-4} \times \text{year}^{-1}$. Naturally, the relative risk ranges widely, but it is the highest for patients with the hereditary form of retinoblastoma and for those with Ewing's sarcoma. The cumulative risk of a secondary sarcoma developing following irradiation for hereditary retinoblastoma at the age of 35 years was 19% (95% confidence interval, 11 to 29) in a series reported from Utrecht, the Netherlands.[5] There are many confounding factors that make interpolation of various radiation sources less than rewarding and not more than a rough approximation. During the first 35 years following exposure to the atomic bomb in Japan, there has been no increase in the incidence of primary malignant bone tumors among the more than 100,000 survivors.[6] These overall estimates by necessity do not quantitate the true risk of postradiation sarcoma, but at least they indicate its order of magnitude.

Most malignant bone tumors occur spontaneously, but on occasion they may develop from other benign tumors and they may follow as a direct consequence of previous radiation therapy. To wit, approximately 5.5% of all osteogenic sarcomas and 15.4% of all malignant fibrous histiocytomas of bone diagnosed and treated at Memorial Sloan-Kettering Cancer Center arose as a result of irradiation.[1,7,8] Postradiation bone sarcomas make up an infrequent but important segment of malignant bone tumors, particularly among adults.[9] These sarcomas represent, together with Paget's sarcomas, the most frequent secondary malignant tumors of bone.[10] It is also fair to say that the number of postradiation tumors will undoubtedly increase especially due to the expected rise in the number of patients who survive longer free of their primary disease but who have to confront this treatment-related disease, "the iatrogenic disease of success."[11]

Most successful treatment approaches in the management of various malignant tumors are multidisciplinary—a combination of radiation therapy, surgery, and adjuvant or even neoadjuvant multiple-drug chemotherapy. Although most patients undergoing such multimodal team management approaches undoubtedly benefit in terms of a prolonged disease-free survival, a shortening of the latent period for the appearance of a second cancer may have to be reckoned with. A heightened risk of postradiation sarcoma under such circumstances is not too farfetched a possibility since patients are likely to live longer.[12,13] There is also the possibility of a

synergistic or additive carcinogenic effect of two or more therapeutic agents.[14-18]

To estimate the relative risk of a second solid cancer following treatment of Hodgkin's disease, a survey emanating from McGill University in Montreal, Canada, pooled the data from seven studies for patients treated by radiotherapy, with or without chemotherapy, and those treated solely by chemotherapy.[19] For all patients with Hodgkin's disease, the relative risk of a second solid cancer developing was 2.1 (95% confidence limits: 1.8 to 2.4). The increased relative risk of a secondary sarcoma developing in bones and soft tissues was especially apparent in this study. Interestingly, those patients who had only chemotherapy for Hodgkin's disease showed no elevated relative risks for secondary cancers, which may be explained at least partly by the relatively shorter duration of follow-up information available for this group of patients. The study by Tucker and co-workers also attempted to evaluate the relative risks of sarcomas developing following chemotherapy alone or chemotherapy coupled with irradiation.[4] A close analysis of the epidemiologic data failed to find proof that chemotherapy using alkylating agents in this clinical setting appreciably enhanced the incidence of a second cancer. This lack of correlation was considered to be due to the relatively few cases under consideration and the limited follow-up time period.

The development of bone and soft tissue sarcoma in patients successfully treated by irradiation for a preexistent benign or malignant lesion is being reported with increasing frequency.[20-23] There are several plausible explanations offered for this. One major reason is the increasing awareness in identifying secondary cancers following successful therapy for another type of tumor—that is, to reach a specific and appropriate definition of what is meant by postradiation cancer. This was initially defined in 1948 by Cahan and associates: the patient received irradiation; the neoplasm occurred in the field of radiation; a latent period of years had elapsed; the original tumor was histologically identified; and the sarcoma is proved on microscopic examination.[24]

The number of sarcomas linked to radiotherapy is likely to increase because of the major successes achieved in the treatment of the primary tumors. That is, patients survive longer, thereby allowing more time for the development of a secondary cancer. Improving survival achieved by intensive therapy may result in side effects, one of the most feared of which is the occurrence of a second cancer. Illustrative of this is the increasing number of sarcomas following the treatment of Hodgkin's disease.[7,19]

Depending on the series of cases reported, the ages of the patients at the time of radiation therapy varied greatly, but at Memorial Sloan-Kettering Cancer Center they ranged from 6 months to 59 years with a mean age of 24 years. At the time of the diagnosis of the sarcoma, the ages of the patients ranged from 9 to 75 years with a mean of 38 and a median of 36 years. Postradiation osteogenic sarcomas developed in 27% of all patients during the sixth decade of life. Other series include more children.[4]

In most instances (64%) the sarcoma arises in patients whose skeleton had been normal at the time radiation commenced, and the osseous structures were only incidentally irradiated. In the others, radiation is aimed at an osseous tumor. The most common bone tumors treated by irradiation are giant cell tumors and Ewing's sarcomas. The reasons for the radiation directed against primary nonosseous conditions are Hodgkin's disease, carcinomas of breast and cervix, and the hereditary form of retinoblastoma.

Although any bone or extraosseous site can give rise to a postradiation sarcoma, the most common osseous sites are the femur and the humerus. The bones of the pelvic and shoulder girdles are involved less frequently, and the craniofacial bones are even rarer sites. Nearly half of all osteogenic sarcomas of the skull arise either in association with Paget's disease of bone or are secondary to irradiation.[10] Similarly to the case discussed in this issue's clinicopathologic conference, a postradiation osteogenic sarcoma developed in the frontal bone after a latency period of 36 years following surgical treatment and postoperative irradiation (48 Gy) for a brain tumor.[25] The most frequent postradiation soft tissue sarcomas are located in the nasal cavity, the neck, the shoulder, the chest wall, the upper arm, the back, and the groin.

The skeletal distribution pattern of postradiation sarcomas shows significant regional and site preferences. Whereas the spontaneously arising osteogenic sarcomas cluster in the knee region (50%), the bones of the pelvic and the shoulder girdles are the preferentially involved sites of the postradiation series. The distal end of the femur is the most common location in the naturally occurring lesions, in contrast to those associated with previous irradiation, where the upper end of the same bone is the preferred site. The relative frequency of the flat bones as sites of postradiation sarcoma, especially the craniofacial and the pelvic bones as well as the sternum, is of note.

Not only osteogenic sarcomas are seen following irradiation, but malignant fibrous histiocytomas, chondrosarcomas, and fibrosarcomas can arise as well.[8] A survey of bone sarcomas linked to radiotherapy in children reports an unusually high incidence (17%) of postradiation chondrosarcomas.[4] This is probably due to the inclusion of cartilage-producing osteogenic sarcomas into this group of tumors.

The mean radiation dose for postradiation bone sarcoma is 6,040 rads, the median dose is 5,700 rads, and the range is 2,500 to 15,000 rads. There is a direct relationship between rising radiation dose levels and the relative risk of postradiation bone cancer developing.[4] The risk clearly increases with increasing radiation dosages.[26] In osteogenic sarcoma the time interval between irradiation and the development of the soft tissue and bone sarcomas varies from 3.5 to 33 years, with a mean of 12.8 and a median of 10 years. This period of latency ranges from 6 to 24 years, with a mean of 11.3 years and a median of 9 years in patients in whom extraosseous sarcomas develop as compared with a range of 3.5 to 33 years, with a mean of 13 years and a median of 10 years of those with osseous osteogenic sarcomas.[1]

The latent period varies from a mean of 8.7 years in children and adolescents (16 years old or younger) to 13.5 years in adults with both osseous and extraosseous osteogenic sarcomas ($P = .02$). Excluding the nonosseous sarcomas, the mean latent period ranges from 8.3 years in children and adolescents (16 years or younger) to 13.8 years in adults ($P = .02$). In view of these figures, there are significantly shorter mean latent periods in patients 16 years or younger in contrast to those who are older than 16 years. The same conclusion is shared for both the osseous and the combination of osseous and soft tissue sarcomas.

True to expectations, the survival of patients in whom postradiation sarcomas develop is poor. The cumulative dis-

ease-free survival rate at five years is 17%, with an estimated median survival of one year. In the field of postradiation sarcomas, the past few decades turned out to be both good and bad. While scores of new cases have been recognized and added to the literature showing that treatment casts long shadows, in turn there was a definite improvement in the understanding of the causes, with a steady accumulation of knowledge of these rare malignant neoplasms. All of this should not arouse undue emotions and make us overly suspicious that the bugbear of a sarcoma lurks behind every irradiated patient. Instead, the occasional appearance of a secondary cancer arising in a field of irradiation should give one pause for thought and impose some restraint in the treatment planning that involves this therapeutic modality.

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Stress and Tension in Patient Care

PHYSICIANS TRADITIONALLY THINK of patient care as a relationship of trust and confidence between physician and patient. This has long been enshrined, in the minds of physicians at least, as the hallowed doctor-patient relationship. It extends, though sometimes to a lesser extent, to the relationship of other health care providers to their patients or clients. In any case, a physician, a patient, and whatever it is that takes place between them are at the true heart of patient care. There can be no doubt that this relationship of trust and confidence is being seriously eroded. There are new stresses on physicians, on patients, and on the relationships between them. Many new tensions are developing in this formerly trusting heartland of patient care, and one can readily suspect that there may be some adverse effects. So far this has received very little study or attention. But wherever there are stresses and tensions, the result is often uncertainty, anxiety, and tension, and these can erode trust and confidence.

The stresses on physicians are familiar, but they are increasing. There is always the stress of a difficult case, and there is the ever-increasing stress of trying to keep pace with the rapid progress in medical science and technology. There are growing tensions in relationships between physicians and the hospitals where they do much of their work, and, of course, there are stresses with third party payers of the care that physicians give, no matter what the system of practice. And perhaps physicians see the most anxiety producing of all to be the ever-present spectre of malpractice litigation, which makes their every action subject to review and criticism. This is at best unsettling; at worst, it makes every patient a potential adversary in a court of law.

There are also stresses—many of them relatively new—on patients. More of the responsibility for what is done or not done in patient care is being placed on patients. Some are eagerly assuming most of the responsibility for their own care. The legal doctrine of informed consent simplistically expects that every patient can be made so fully informed about his or her condition and the options for diagnosis and treatment that patient, not physician, theoretically becomes the one more competent to make the final decision as to what is to be done. While conceptually this may be ideal and desirable, in practice it can prove stressful for many patients, particularly when anxiety and fear of what they can never know and do not understand may already be present. For example, some states now require that all the options for diagnosing and treating cancer of the breast be explained to a patient, who must then decide herself what to do at a time when she is almost always under severe emotional stress and seeking help and advice. The media often contribute unwittingly to patient stress and anxiety. Horror stories of patient care gone wrong are vividly reported and frequently given repeated coverage, with little consideration for readers who may apply the horrific possibilities to their own situation, thus adding considerably to their perhaps already heavy burden of fear and anxiety.

The most stress producing of all for patients and their families may be the apparent lessening of the confidence of society as a whole in physicians and the medical profession. Rightly or wrongly, documented or not, and consciously or unconsciously, this lessening of confidence and trust is becoming very real, and it is beginning to produce new stresses and tensions in doctor-patient relationships. The traditional

trust and confidence are being eroded, resulting in effects on patient care that have yet to be understood or evaluated. Certainly, lack of trust and lack of confidence are anxiety producing, and we know that stress and tension do not usually help to assure health or speedy recovery from illness. For example, lack of trust and confidence may affect such a simple thing as a patient's compliance with an agreed upon treatment program, with a resulting adverse effect on a patient's care outcome.

Stress and tension in patient care are facts of everyday life in today's health care environment. They add relatively new dimensions to every physician-patient relationship. This deserves attention. A physician should be aware of his or her own concerns and should try to discover the fears, concerns, and anxieties of a patient. In any individual case, the diagnosis and treatment of stress and tension in the doctor-patient relationship may be fully as important as understanding and treating the illness for which the patient seeks help. Both physician and patient are finding themselves in new roles to which each must adapt, but the heart of medical practice remains the same. It still is what takes place in the interaction between physician and patient, and it still is the patient who seeks help and the physician who uses the art and science of the profession to give the help that is needed. At its best this heart of medical practice can transcend much of these new stresses and tensions.

MSMW

Case Reports

Mycotic Aneurysm and Disseminated *Mycobacterium avium-intracellulare* Infection in a Patient With Hairy Cell Leukemia

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HAIRY CELL LEUKEMIA is a lymphoproliferative disorder characterized by pancytopenia, an indolent course, and susceptibility to infections normally controlled by the cell-mediated immune system. Infection by nontuberculous mycobacteria occurs in 5% of patients with hairy cell leukemia and is frequently disseminated with a fatal outcome.[1] In this report, we describe a patient with hairy cell leukemia whose disseminated *Mycobacterium avium-intracellulare* infection had a unique site of symptomatic involvement, the popliteal artery, that resulted in a mycotic aneurysm.

Report of a Case

The patient, a 58-year-old man, was seen because for two months he had had fever, weight loss, and progressive swelling and pain in the right calf and popliteal fossa. Nine years before admission, he had suffered a right leg injury requiring several reconstructive procedures. Four years before admission, mild pancytopenia was noted, and hairy cell leukemia was diagnosed by bone marrow examination that showed typical hairy cells containing tartrate-resistant acid phosphatase. At the time of hospital admission, he had hepatosplenomegaly and right calf tenderness with edema and erythema but no palpable mass or cord. The leukocyte count was 0.6×10^9 per liter with 0.48 neutrophils and no monocytes. The hematocrit was 0.2 and the platelet count was 104×10^9 per liter. A chest radiograph showed no pulmonary infiltrates, cavities, or effusions. The patient was anergic to intradermal skin tests. Fever occurred 12 hours after admission, and broad-spectrum antibiotics were given. Daily fevers to 38°C to 39°C (100.4°F to 102.2°F) were noted. After six days, cultures of specimens of blood, sputum, urine, and cerebrospinal fluid were all negative, and antibiotic therapy was discontinued. A pulsatile right popliteal mass developed. Cultures of specimens of blood from peripheral and right femoral veins were negative.

On the eighth hospital day a splenectomy was done. The liver, spleen, and bone marrow were infiltrated by hairy cells, but neither acid-fast bacilli nor granulomata were seen. The fever continued and, postoperatively, bacteremia with *Staphylococcus aureus* was recorded. The popliteal mass enlarged, and on the 14th hospital day, a popliteal aneurysm was resected and a saphenous vein bypass graft done. After the operation, *S aureus* was cultured from the aneurysm. On the 36th hospital day, *M avium-intracellulare* grew in cultures of the liver, spleen, and bone marrow. On reexamination of the mycotic aneurysm, acid-fast bacilli were visible microscopically (Figure 1) and *M avium-intracellulare* grew from specimens of both the aneurysm and peripheral blood.

Therapy with isoniazid, rifampin, ethambutol hydrochloride, and streptomycin was begun, but arterial hemorrhage occurred in the right popliteal space, requiring an above-the-knee amputation. The patient's daily fever gradually resolved, and on the 46th hospital day, rifampin was replaced by ansamycin, 150 mg given orally per day. Subsequent antimicrobial susceptibility testing showed sensitivity to ansamycin, 2 μg per ml; isoniazid, 5 μg per ml; streptomycin, 10 μg per ml; and cycloserine, 30 μg per ml. By the 56th hospital day, he was afebrile, and, after rehabilitation, was discharged from the hospital.

Seven months after discharge, a pulsatile right groin mass was noted, and a 3-cm pseudoaneurysm was resected from the site of the previous proximal saphenous vein graft anastamosis. *M avium-intracellulare* grew from a specimen of this material. The organism was susceptible only to ansamycin, 2

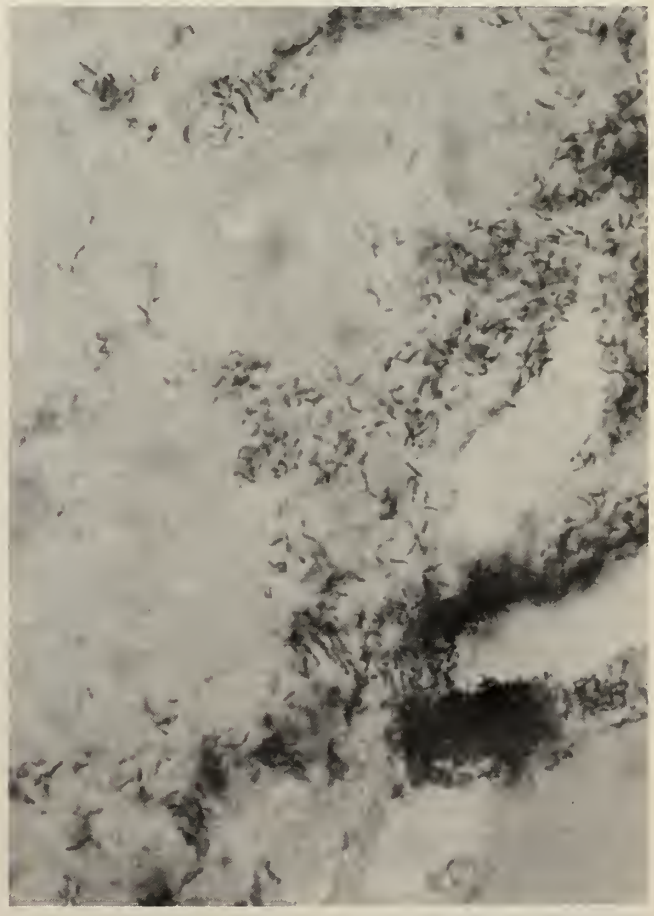

Figure 1.—A specimen of the wall of mycotic aneurysm shows acid-fast bacilli (Ziehl-Neelsen stain, original magnification × 1,000).

(Dugdale DC, Stevens DL, Knight LL: Mycotic aneurysm and disseminated *Mycobacterium avium-intracellulare* infection in a patient with hairy cell leukemia. West J Med 1989 Feb; 150:207-208)

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μg per ml, and the streptomycin therapy was discontinued. The patient remains afebrile, and after two years of antimycobacterial therapy, the leukocyte count is 5.8×10^9 per liter, the hematocrit is 0.48, and the platelet count is 330×10^9 per liter.

Discussion

This patient is unique among other patients with hairy cell leukemia and disseminated *M avium-intracellulare* infection because he had a mycotic aneurysm caused by the organism. In the past, mycotic aneurysms were mostly a complication of endocarditis or atherosclerosis; at present they are usually a complication of trauma. In a recent series *S aureus* and *Enterobacter* were the most common pathogens,[2] though tuberculous aneurysms of the aorta have also been reported.[3,4] Approximately 1% of popliteal aneurysms are mycotic aneurysms.[5] *M avium-intracellulare* has not been previously reported as a causative agent of these aneurysms.

The source of the mycobacterial bacilli in our patient is unknown. In a recent series,[1] eight of nine patients with hairy cell leukemia and disseminated nontuberculous mycobacteriosis had abnormalities on chest radiography presumed to represent the source of infection. In contrast, our patient's lack of a demonstrable pulmonary focus together with the preexisting contaminated compound fracture of the femur raise the possibility, however speculative, that the leg was the source of infection of this saprophytic organism.

Disseminated nontuberculous mycobacterial infection occurs in 5% of all infections due to nontuberculous mycobacteria.[6] Most adults with disseminated *M avium-intracellulare* have a previously diagnosed immunosuppressive disorder,[7] and hairy cell leukemia is present in 5%. Disseminated *M avium-intracellulare* has been reported in a significant number of patients with the acquired immunodeficiency syndrome.[8] Studies of patients with malignant disease[9] and hairy cell leukemia[1,10-13] have concluded that *Mycobacterium kansasii* is the most common nontuberculous mycobacterial pathogen, though the frequency has considerable geographic variation, presumably related to the geographic distribution of the natural bacterial reservoirs. Theories concerning the predilection of nontuberculous mycobacterial infection for patients with hairy cell leukemia have focused on the nature of the host defense to intracellular pathogens. Although skin test responses are generally intact in patients with hairy cell leukemia,[13] profound monocytopenia is commonly seen. The pathologic features are often remarkable, as in the present case, for a lack of granuloma formation and a predominately granulocytic response.

Recurrence or relapse of infection is common in patients with disseminated *M avium-intracellulare* infection with the acquired immunodeficiency syndrome.[8] Local recurrence or persistence of mycobacteria at a site is uncommon, however. In our patient, persistence could be related to anatomic factors related to the presence of a thrombosed venigraft that had traversed the primary infected site, host-defense deficiency due to hairy cell leukemia, or the development of antimicrobial resistance. Because a second disseminated mycobacterial infection did not develop while the patient was being treated, and in view of his subsequent course following surgical procedures, we speculate that the anatomic factor was the most important.

Disseminated nontuberculous mycobacterial infection will develop in 5% of patients with hairy cell leukemia, and 20% of these cases are due to *M avium-intracellulare.*[1] Although mycobacterial infection is clearly not a common complication of hairy cell leukemia, it is treatable and is often a difficult diagnostic challenge. With the continued rise in the number of immunocompromised patients, infection with *M avium-intracellulare* is likely to be recognized more frequently.

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Fatal *Pasteurella multocida* Pneumonia in an IgA-Deficient Cat Fancier

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Pasteurella multocida is a ubiquitous organism well known to veterinarians as a commensal and opportunistic pathogen; it is commonly present in the mouths of healthy dogs and cats.[1] In humans, *P multocida* infections are most commonly seen by emergency department physicians who treat animal bites and scratches, but the incidence of such infections is underestimated because of a lack of clinical suspicion and of appropriate bacteriologic investigation.[2,3] The clinical manifestations of *P multocida* infections have been succinctly described by Beyt,[4] and in a comprehensive review, Weber and co-workers also divide *P multocida* infections into three groups[5]: infection from animal bites and scratches, which may progress to cause serious local complications; respiratory tract disease including pneumonia, lung abscess, and

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TABLE 1.—*Bacteriologic Studies in a 46-Year-Old Patient With* Pasteurella multocida *Pneumonia and in His 5 Domestic Cats**

Subject	Organism	Source of Specimen			Capsule	Reaction to Heddelston's 'Somatic' Type 3 Serum	Fermentation	
							Glycerol	Sorbitol
Patient	*P multocida*	Sputum			No	Pos	Pos	Pos
		Nose/throat/trachea						
Cats								
A	*P multocida*	Neg	Pos	Neg	No	Pos	Pos	Pos
B	*P multocida*	Neg	Pos	Pos	No	Pos	Pos	Pos
C	*Pasteurella pneumotropica*	...	...	...	...	...	...	...
D	*P pneumotropica*	...	...	...	...	...	...	...
E†	.....	...	...	..	...	...	...	...

Neg=negative, Pos=positive

*These findings by courtesy of G. R. Carter, DVM, of Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, Virginia

†Not *Pasteurella*—probably either *Acinetobacter* or *Moraxella*.

empyema; and other systemic illness including bacteremia, cerebral abscess and meningitis, spontaneous peritonitis, and intra-abdominal abscess.

We describe the case of a patient with bronchiectasis and immunoglobulin (Ig) A deficiency in whom fatal *P multocida* pneumonia developed, and we present evidence that the infection originated from nontraumatic contact with domestic cats.

Report of a Case

The patient, a 46-year-old paper mill worker, was referred for evaluation of chronic productive cough, repeated respiratory tract infections since adolescence, and intermittent hemoptysis. On physical examination he had chronic dental sepsis, finger clubbing, and crackles over both lungs. An IgA level was 0.37 grams per liter (normal range, 0.87 to 3.85). IgA deficiency had previously been identified in his 16-year-old daughter. Extensive bilateral varicose bronchiectasis was shown on bronchography. No pathogens were identified in a sputum culture. Notable improvement occurred with chest physiotherapy and antibiotic therapy, and the patient went back to work.

Five months later he returned complaining of weakness, anorexia, and a 10-kg (22-lb) weight loss over six weeks. About a month earlier he had been bitten by one of his five cats, but no local lesion had developed. Chest radiographs showed evidence of extensive bilateral pneumonia. A Gram's stain showed polymorphonuclear leukocytes and gram-negative bacilli. Repeated sputum cultures consistently yielded *P multocida,* and no antibiotic resistance was noted on susceptibility studies. Blood cultures were negative. A leukocyte count was 13.8×10^9 per liter with neutrophilia and toxic granulation. The hemoglobin level was 100 grams per liter. The hemoglobin value had been normal on the previous admission. Anergy was shown on skin testing with multiple antigens. The initial treatment included frequent postural drainage, nutritional supplements, and the administration of tetracycline. Intravenous cefazolin was also given. Penicillin was not given at first because of a history of penicillin allergy. Following desensitization, intravenous penicillin, 20 million units per day, was administered, with elimination of *P multocida* from sputum specimens thereafter. Despite clearing of the infection and hyperalimentation, the patient's condition deteriorated with the development of ventilatory failure and further respiratory tract infection *(Klebsiella, Enterobacter, Pseudomonas)* leading to death 11 weeks after admission. Necropsy findings confirmed the presence of bilateral bronchiectasis together with organizing bronchopneumonia. Postmortem cultures of the lung were negative for *Pasteurella.*

Shortly after the patient's admission, a home visit was made to obtain bacteriologic swabs from the family cats. The five cats, which were all healthy, showed some feral rather than domestic traits, and one eluded examination. The findings of gum and throat swab specimens on the other four proved normal. Because of the severe illness of the patient and the deemed hazard to his 16-year-old IgA-deficient daughter, the family agreed to having the cats impounded. Further bacteriologic studies were done (Table 1). Cultures from two of the cats yielded *Pasteurella pneumotropica,* and no *Pasteurella* species were identified in a third. The other two cats yielded a strain of *P multocida* with similar characteristics to that identified in the patient. It was concluded that the patient's *P multocida* infection derived from one or both of these two cats. One of these (cat A) had bitten the patient a month before his admission to hospital.

Discussion

Infections with *P multocida* form one of the bacteriologically heterogeneous group of zoonoses that, in the definition of the World Health Organization, comprise those diseases and infections that are naturally transmitted between other vertebral animals and humans.[6] In their review of *P multocida* infections that included 34 personal cases, Weber and associates record 25 well-documented cases of *P multocida* pneumonia.[5] Most patients had underlying lung disease, including three with bronchiectasis. Nine patients died, five of respiratory failure occurring three to six weeks after the beginning of treatment. The extent of underlying pulmonary disease likely contributes to the high mortality, and most patients with respiratory tract infections have a history of animal exposure. It is exceptional for a contact history not to be obtained if sought. A unique outbreak of *P multocida* infection occurred in a chronic-disease hospital where epidemiologic studies failed to determine the source.[7]

No evidence of local reaction (cellulitis, suppuration, or adenitis) developed at the site of a cat bite sustained by our patient, and he probably acquired the infection by inhalation.

P multocida was subsequently recovered from the throat of the cat that inflicted the bite (cat A), but the onset of illness antedated the injury. The colonization or infection of the human respiratory tract by *P multocida* is most commonly associated with atraumatic animal exposure resulting in airborne or direct transmission. In a recent review of pet-associated illness,[8] the hazards and the management of animal bites are described with particular reference to *P multocida* as a pathogen, but atraumatic infections[9] are not mentioned. Because *P multocida* has a predilection for patients with impaired host defenses, such patients should avoid close contact with domestic pets. Such close contact may involve kissing or nuzzling or being licked by the pets. *P multocida* causing subdural empyema has been described in a patient with a history of ethmoid polypectomy who kissed her dog and two cats.[10,11] Joint infection associated with rheumatoid arthritis and prostheses may be contracted by pet owners,[12,13] as may appendiceal peritonitis[14] and spontaneous peritonitis associated with hepatic cirrhosis.[15] Where contact is close or a person susceptible, or both, it may not be necessary for puncture or abrasion of the skin to occur.[16,17] Thus, a report of a 60-year-old patient with meningitis who regularly kissed her pet mongrel includes a specific warning that pets should not be kissed.[18] Further to this point, Clapp and colleagues regard *P multocida* meningitis in infants as a disease that may be prevented by advising parents not to allow their infants to be licked by household pets.[19] The inoculation of fur by *P multocida* in saliva during grooming is a further hazard to infants in close contact with pets and presumably also to susceptible owners who nuzzle their pets.[20]

Respiratory symptoms develop in only a few patients who have IgA deficiency. Those who have respiratory tract illness appear to be at particular risk for *P multocida* infections developing, as is the case with persons with cirrhosis of the liver or chronic joint disease, during infancy, and in pregnancy.[21] In general, the benefits of pet ownership far outweigh the disadvantages, but if pets are recommended by physicians as therapeutic aids,[22] then due attention and advice should be given regarding the risk and prevention of zoonotic infections including those caused by *P multocida*. Patients with IgA deficiency and respiratory tract symptoms should be urged to avoid close contact with cats and dogs.

Further, the occurrence of infection in susceptible persons who are pet owners should give rise to the suspicion that zoonotic infectious agents such as *P multocida* or the DF-2 bacillus may be responsible.[23] Both organisms are commensals in dogs and cats[1,24] and are more likely to cause serious disease in patients with impaired host defenses against infection.[5,25] Unless there has been injury, a history of contact with animals may not be volunteered. If there is a suspicion of such zoonotic infection, detailed bacteriologic investigation and prompt treatment with penicillin should be initiated. "Those who'll play with cats must expect to be scratched" (Cervantes, *Don Quixote*), but it is clear that even nontraumatic contact with cats may give rise to serious and sometimes fatal illness.

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Fatal Hyperthermia Associated With Cocaine Use

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RECREATIONAL COCAINE USE has been associated with multiple medical complications, particularly cardiovascular and central nervous system dysfunction.[1] We report two cases of fatal cocaine-associated hyperthermia.

Report of Cases

Case 1

The patient, a 30-year-old man, presented to the Harborview Medical Center (Seattle) Emergency Department following a witnessed seizure, which occurred three to four hours after the intravenous administration of cocaine. His

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medical history was significant for heroin and cocaine abuse, including cocaine-associated seizures.

On arrival, the patient was agitated, diaphoretic, and alert. His temperature by axilla was 38°C (100.4°F), blood pressure 90/60 mm of mercury, heart rate 155 per minute, and respirations 20. The results of his initial examination were otherwise unremarkable. The initial laboratory values included a serum sodium of 151 mmol per liter, potassium 5.0 mmol per liter, chloride 111 mmol per liter, bicarbonate 23 mmol per liter, blood urea nitrogen 5.4 mmol per liter of urea (15 mg per dl), creatinine 190 μmol per liter (2.1 mg per dl), and glucose 5.1 mmol per liter (92 mg per dl). The hematocrit was 0.52, leukocyte count 7.8×10^9 per liter, and platelet count 281×10^9 per liter. A blood smear showed atypical lymphocytes with budding nuclei, but the findings were otherwise normal. Three hours later a prothrombin time was 15.4 seconds (control 12.0 seconds), partial thromboplastin time 45 seconds (range 26 to 42), fibrin degradation products greater than 2,000 ng per ml (normal <200), fibrinogen 161 mg per dl (normal 150 to 400), and the thrombin time was 35 seconds (normal 18 to 28). The platelet count was not repeated.

The patient had two generalized seizures 50 minutes after arrival. His temperature by rectum was 43°C (109°F) 45 minutes after the seizures. Bradycardia and ventricular arrhythmias resulted in hypotension, requiring intubation and the administration of pressors. He was placed on a cooling blanket, and ice packs were placed over his major arteries. An hour later his temperature was 38.6°C (101.5°F). The results of repeat laboratory studies were remarkable for a serum sodium of 159 mmol per liter, a potassium of 6.9 mmol per liter, chloride 104 mmol per liter, bicarbonate 18 mmol per liter, creatinine 265 μmol per liter (3.0 mg per dl), ionized calcium 1.94 mmol per liter (normal 2.32 to 2.58), and phosphate 3.75 mmol per liter (normal 0.97 to 1.45). The creatine kinase level was 14,090 units per liter (normal <100), the lactic dehydrogenase level was 2,170 units per liter (normal <304), and urine myoglobin more than 5,000 ng per ml. A gastric toxicologic screen was positive for nicotine metabolites and cocaine and negative for other drugs such as amphetamine, atropine, barbiturates, phenothiazines, phencyclidine hydrochloride (PCP), narcotics, mescaline, and methaqualone. A serum toxicology screen was negative for salicylate, acetaminophen, sedatives, hypnotics, and volatiles. An electrocardiogram showed ST segment depression in the inferior leads. A chest x-ray film showed the lungs to be clear.

The patient became anuric, more hyperkalemic, and remained hypotensive despite pressor support. Signs of pericardial tamponade developed, and a pericardiocentesis yielded 25 ml of bloody fluid. Five hours after presenting to the emergency department, he died. An autopsy showed 600 ml of bloody pericardial fluid and hemorrhage, congestion, and atelectasis in the lungs. Blood and urine cultures were negative. A drug screen of a serum specimen taken at the time of the autopsy was negative for cocaine but positive for benzoylecgonine, a cocaine metabolite. No drugs, including cocaine metabolites, were detected on an autopsy urine screen.

Case 2

A 38-year-old known cocaine user was brought to the Harborview Emergency Department by police. He had been acting bizarrely and barking like a dog. The patient was agitated, diaphoretic, incoherent, and unresponsive to pain. His blood pressure was 120/69 mm of mercury, his pulse was 150 per minute, respirations 40, and temperature 41.1°C (106°F). The precordium was hyperdynamic and a grade II/VI nonradiating systolic murmur was auscultated. There were old needle marks on the extremities, and a stool specimen was guaiac-positive.

Initial laboratory values were remarkable for a serum sodium of 144 mmol per liter, a potassium of 5.1 mmol per liter, a chloride of 105 mmol per liter, a bicarbonate of 11 mmol per liter, and an anion gap of 18. A blood urea nitrogen level was 6.1 mmol per liter of urea (17 mg per dl), and creatinine was 190 μmol per liter (2.2 mg per dl). Arterial blood gas values determined while the patient was breathing room air were a pH of 7.31, a partial oxygen pressure of 61 torr, and a partial carbon dioxide pressure of 26 torr. A leukocyte count was 9×10^9 per liter, hematocrit 0.48, and platelets 145×10^9 per liter. A blood smear showed slight poikilocytosis and hypersegmented polymorphonuclear leukocytes. The prothrombin time was 19.9 seconds, partial thromboplastin time 79 seconds, thrombin time 50 seconds, fibrinogen level 108 mg per dl, and fibrin degradation products more than 2,000 ng per ml. The serum aspartate aminotransferase level was 1,535 units per liter (normal <25), the alanine aminotransferase was 1,155 units per liter (normal <30), lactic dehydrogenase 7,480 units per liter (normal <290), and creatine kinase 17,040 units per liter. A urine myoglobin level was more than 5,000 ng per dl. A lumbar puncture showed an opening pressure of 500 mm of water and 9 erythrocytes. A urine toxicology screen was positive only for cocaine and cocaine metabolites and nicotine and metabolite; a gastric screen was negative for cocaine, as well as for other drugs (those mentioned in case 1).

An endotracheal tube was introduced, and the patient was cooled with gastric lavage to normal body temperature. Broad-spectrum antibiotics were administered. Massive gastrointestinal and nasal bleeding was associated with a partial thromboplastin time of longer than 200 seconds, a fibrinogen level of less than 5 mg per dl, fibrin degradation products of more than 2,000 ng per ml, and a platelet count of 25×10^9 per liter. Hypotension ensued, as did anuric renal failure. The creatine kinase level peaked at 30,000 units per liter, and persistent hypoglycemia required an infusion of a solution of 50% glucose in water. Hemodynamic and hematologic stability was obtained but the patient remained unresponsive, with renal and hepatic failure. On hospital day 7, a total bilirubin level was 422 mmol per liter (24.7 mg per dl) and creatinine 870 μmol per liter (9.8 mg per dl). The patient died after ventilator support was discontinued. Urine and cerebrospinal fluid cultures were negative. One blood culture was positive for coagulase-negative staphylococci (in aerobic broth).

Discussion

We describe two cases of cocaine-associated hyperthermia that resulted in death. Both patients were known cocaine users whose toxicologic screens were positive only for cocaine and nicotine and negative for other drugs or toxins. The cases are similar in that both presented with fever greater than 40°C (104°F) early in the evaluation, diaphoresis, tachycardia, tachypnea, and altered mental state. The results of laboratory tests were remarkable for metabolic

acidosis, bleeding due to coagulopathy, anuric renal failure with rhabdomyolysis, and a dramatic elevation of muscle and liver enzymes.

The clinical findings are consistent with described cases of heatstroke.[2] In a review of 36 patients, all were young men engaged in physical exercise. There was no description of drug use. Eight of the cases were fatal, characterized by convulsions, prolonged unconsciousness, hypernatremia, oliguric renal failure, evolving disseminated intravascular coagulation, and elevated liver enzymes.

In addition, these patients had manifestations similar to those of other patients with drug-associated hyperthermia.[3] Rosenberg and co-workers described 12 patients with hyperthermia due to anticholinergic agents, central nervous system stimulants, salicylates, or a combination of drugs. Manifestations included coma (11/12), increased muscle activity before hyperthermia (9/12), seizures (5/12), rhabdomyolysis (6/12), hypotension (8/12), coagulopathy (5/12), and acidosis (11/12). Five patients died, and four patients had permanent neurologic sequelae.

While hyperthermia has been associated with a variety of drug intoxications,[3] its association with cocaine use has not been well documented until recently. We found two cases of apparent cocaine-induced hyperthermia previously reported in the literature.[3,4] Toxicologic screens were negative for cocaine in both, however, and in one case the screen was positive for methadone, amitriptyline, and ethanol. Both patients survived. In addition, fatal malignant hyperthermia has been described in a 20-year-old man after recreational cocaine and ethanol use.[5] This patient had a history of being susceptible to malignant hyperthermia and a family history of the same. Our patients both had a history of known cocaine use, had toxicologic screens positive for cocaine, and were found free of other drugs and metabolites. In addition, no evidence of infection as a possible cause of fever was found despite several cultures. Thus, the hyperthermia was strongly associated with intravenous cocaine use in these patients.

In the past year or two, three cases of hyperthermia, rhabdomyolysis, and acute renal failure associated with cocaine use have been reported.[6-8] The patients presented with agitation, an altered mental state, and tachycardia. Toxicologic screens confirmed the presence of cocaine (or its metabolite) in all cases. These three patients survived, renal function improved, and they were discharged from hospital.

Our patients, in addition to manifesting hyperthermia, rhabdomyolysis, and renal failure, had coagulopathy and fatal outcome. Patient 2 had hepatic failure and remained unresponsive despite a correction of hemodynamic and laboratory values.

Our two patients had a clinical course similar to that of patients afflicted by heatstroke.[2] We suggest that cocaine-associated hyperthermia may be a primary cause of various clinical toxic reactions associated with cocaine use. These toxic effects include rhabdomyolysis, renal failure, liver enzyme elevation, obtundation, and coagulopathy. Our hypothesis is supported by a study of cocaine intoxication in dogs.[9] Cocaine was administered intravenously to dogs. Hemodynamic, clinical, and metabolic indices were controlled with pharmacologic pretreatment. The effects of hyperthermia on the clinical outcome were evaluated, and it was found to be the most important factor associated with a fatal outcome.

Hyperthermia due to cocaine intoxication is probably multifactorial and includes increased muscle activity, seizures, an increased metabolic rate from increased sympathetic nervous system activity, and impaired heat loss from peripheral vasoconstriction.[3,6,10] Therapy is directed at rapidly lowering the body temperature to prevent irreversible cellular injury. Suggested measures to lower the body temperature include a cooling blanket, convection evaporation,[11] intubation with cool air ventilation, and iced saline gastric lavage. As muscular activity is probably a primary cause of hyperthermia, sedation or paralysis may be indicated in certain cases.

Our patients rapidly defervesced without extensive measures. Difficulty in controlling hyperthermia associated with cocaine use may indicate an underlying thermoregulatory dysfunction precipitated by cocaine use or an adulterant. Specifically, findings of muscular rigidity suggest malignant hyperthermia,[5] which might require pharmacologic intervention, such as the use of dantrolene sodium.

Hyperthermia may be a leading contributor to the toxic effects of cocaine use. Aggressive management of this problem is indicated to decrease the toxic effects.

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Correspondence

Seizures Associated With Smoking 'Crack'—A Survey of Adolescent 'Crack' Smokers

To THE EDITOR: The neurologic aspects of cocaine abuse, including a detailed section on cocaine-induced seizures, were discussed comprehensively in the October 1988 issue of the journal.[1] I have just analyzed a survey of 279 mostly middle-class white adolescents who took cocaine before being admitted to one of a chain of private, modified-outpatient drug-abuse treatment facilities. The 279 respondents were subdivided into four groups: 149 adolescents who "snorted" cocaine and never smoked "crack"; 87 who had smoked "crack" 1 to 9 times, designated as experimenters; 20 who had smoked "crack" 10 to 50 times, designated as the intermediate group; and 23 who had smoked "crack" more than 50 times, designated as the heavy-use group.

Approximately 30% of those who "snorted" but never smoked cocaine versus 50% of experimenters, 60% of the intermediate group, and 80% of the heavy-use group responded in the affirmative when queried about signs and symptoms of addictive cocaine use. These included preoccupation with thoughts of cocaine, inability to cut down on amount or frequency of cocaine use, inability to refuse an offer of cocaine, and inability to save leftover cocaine for future use. Brain seizures were noted by 0%, 1%, 10%, and 9% of each of the above groups, respectively ($P < .0001$). Loss of consciousness while smoking "crack" was noted by 2%, 10%, and 30% of the 130 adolescent "crack" smokers.

More than any other drug in widespread use in this country, "crack" cocaine will cause neurologic problems serious enough to bring the user to a physician. Unexplained seizures that occur after age 12 should prompt physicians to order a urine toxicology screen by an immunoassay method, which can detect cocaine in much smaller amounts than the traditional thin-layer chromatography broad spectrum drug screen used by most emergency medicine facilities.

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Treating Neurosyphilis

To THE EDITOR: In his excellent review on neurosyphilis in the July 1988 issue, Dr Kenneth Jordan makes two conclusions that deserve some comments.[1]

Dr Jordan states that the sensitivity of today's cerebrospinal fluid (CSF) VDRL test is much higher than the sensitivity of the classic CSF Wassermann test. The higher sensitivity of the blood VDRL test compared with the blood Wassermann test is well known; however, the flocculation tests in the CSF have been considered less satisfactory than the Wassermann test.[2]

In my experience the CSF Wassermann test done as described by Kolmer and co-workers[3] is more reliable than the CSF VDRL. In an evaluation of 44 patients with active symptomatic neurosyphilis and with positive CSF Wassermann test results, I found 6 patients with false-negative CSF VDRL test results.

Another important conclusion by Dr Jordan is that "the treatment of active neurosyphilis should produce uninterrupted CSF penicillin concentrations of no lower than 0.031 IU per ml for 15 to 21 days." There are strong theoretical data supporting this conclusion, but my many years of clinical experience do not agree with it.

The efficacy of intramuscular penicillin in the treatment of neurosyphilis was witnessed soon after excellent results were reported in the treatment of early syphilis. The penicillin doses used in the treatment of neurosyphilis in those days were low, but treatment failures occurred in about 10% of these patients.[4] It is unlikely that the penicillin levels now proposed as therapeutic had even been attained by the doses used in those first series. So at least 90% of patients with neurosyphilis were successfully treated with penicillin doses now considered insufficient on a theoretical basis. It is possible that other factors are responsible for the treatment failures.

Therapeutic failures in neurosyphilis can occur even after high doses of penicillin are administered. A total of 41 patients with active neurosyphilis were treated in our service with at least 20 million IU of intravenous penicillin daily for 20 days.[5,6] Three patients still had more than 5 cells per μl one year after treatment, and in accordance to Dattner's criteria, they should be considered therapeutic failures.[7] I agree, therefore, with Dr Jordan that "whichever regimen is chosen, careful follow-up is necessary to ensure a cure."

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Neonatal-Perinatal Medicine—A Model Subspecialty

To THE EDITOR: Subspecialization has been the unavoidable consequence of the success of modern medical science. It threatens, in principle, the subjectivity of the patient because of the assignment of expertise according to the categories of understanding related to organ systems, diseases, body parts, procedures, and so forth. The actual performance of services by experts is often limited to practices understood to be relevant to their designated categories of special knowledge. Ironically, in the interest of complete care, the patient is approached as one might approach a complex machine. In many important and convenient ways, the human body en-

courages such an approach, but the patient frequently is incompletely relieved by the most complete mechanistic strategies. Sometimes a disease that is understood to exist can be "cured," yet illness will persist—or vice versa. A "whole body event" might go unappreciated by a too narrowly focused subspecialist.

Neonatal-perinatal medicine, a subspecialty within pediatrics, is also based on a narrowness of focus, but the focus is developmental. Neonatologists have remained physicians for the whole patient (and parents). On a day-to-day basis, we have remained primarily concerned with injury or life-threatening "whole body events" from birth through the first 28 days of life. More recently, we have begun consulting on behalf of the fetus and have become committed to the care of injured newborns for many months after birth. We have, however, by virtue of our focus on development and our appreciation of human illness as situated dysfunction, considered approaches to the care of our patients at all levels, from intracellular phenomena to social events. Nonetheless, neonatologists seem particularly vulnerable to seduction by reductionist theories, not only from the "scientific" perspective, with its promise of preventive medicine for neonatology through developmental biology, but also from the "clinical" perspective, with its promise to fix "anything that does not work the way it should" with some new procedure or piece of equipment—high frequency ventilation, extracorporeal membrane oxygenation, and so forth. In fact, until recently the latter persuasion has threatened the training of the practitioner of scientific medicine in this subspecialty. There has been a proliferation of neonatology trade schools that produced a generation of neonatologists with delusions of omnipotence. Now, there is talk not only of omnipotence but omniscience by a new generation of basic scientists.

It is hoped that we will listen carefully to our colleagues, as we have previously listened to physiologists, pharmacologists, and engineers, willing to learn whatever we can in order to practice scientifically and teach ourselves the applied sciences. When we teach ourselves, however, our education should include not only "re-tooling" research skills and incorporating the information from the basic sciences but also a respect for the ignorance that we still have and for the art of our practice.[1] We will cure if we can and heal because we must—that is a physician's role. I can think of no better place to serve than as a neonatologist—physician for the newborn and the future.

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Items submitted for the Correspondence section should be typed doubled-spaced (including references) with conventional margins. The text should not exceed 600 words.

Seminars in Health Care Delivery

Long-Term Care for the Elderly

The Future of Nursing Homes

BRUCE C. VLADECK, PhD, *New York*

This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

Continuing growth in the number of impaired elderly persons necessitates a continued reliance on nursing homes to care for at least those who are most impaired or most lacking in other supports, despite dissatisfaction over the quality of nursing home services and anxiety about the costs. Nursing home care now costs more than $30 billion annually, half of which comes from governmental sources. The Medicaid program, in particular, is central to all aspects of the nursing home industry. Private long-term care insurance is unlikely to solve the problem of nursing home financing. Rationalizing public expenditures will hinge critically on greater clarity as to just what roles nursing homes are expected to fulfill in the system of care, especially how they are supposed to relate to other services provided to Medicare beneficiaries.

(Vladeck BC: Long-term care for the elderly—The future of nursing homes. West J Med 1989 Feb; 150:215-220)

After years of occupying the "Bermuda triangle" of public policy, nursing homes have once again achieved a prominent place on the political agenda for reasons having little to do with their characteristics or performance. Examining both the current issues surrounding nursing homes and the ways in which they became issues can significantly illuminate attributes of these important facilities, while also helping to characterize some of the basic dilemmas that otherwise receive short shrift in health policy.

Three separate, largely unrelated, series of events have fortuitously intersected to raise the visibility of nursing home issues. The first, which has the most immediate consequences for nursing homes and their residents, culminated at the end of 1987 in the first significant federal legislation on standards of care for nursing homes in 15 years.[1] The chain of events leading to that legislation began with efforts of the then newly elected Reagan Administration in 1981 and 1982 to fulfill its campaign promises of deregulating America's private business sector. The administration announced in 1982 an effort to substantially simplify the regulatory process involving nursing homes and to reduce the regulatory burden on the businesspeople who ran most of them. This initiative engendered a vocal and well-orchestrated response from consumer advocacy groups and their congressional allies. After a couple of years of sparring between the legislative and executive branches, a typical Washington compromise kicked the entire issue of nursing home regulation to the Institute of Medicine (IOM) of the National Academy of Sciences for study.[2(pp 2-3)]

The IOM study, concluded in early 1986, found that nursing homes needed more regulation, not less, and that, in particular, the federal government needed to take a substantially more active and aggressive role in the shared federal-state process that administers most facilities regulation. The IOM study also called for refocusing federal standards on the quality of life as well as the quality of care in nursing homes, for a regulatory process substantially more sensitive and responsive to the characteristics and concerns of individual residents and their families, and for more targeted and sophisticated inspection and sanctions processes. After almost two years of further sparring between Congress and the executive branch, the principal recommendations of the IOM study were enacted into law.[2(pp 25-44)]

The second series of events that almost inadvertently brought nursing home issues to broader attention originated with the appointment of Otis Bowen as Secretary of the Department of Health and Human Services in 1985. Dr Bowen, who was appointed to that position at least in part because of his deserved reputation as a political and fiscal conservative, brought to the office a deep personal commitment to expanding the protection of Medicare beneficiaries against the costs of catastrophic illnesses. Armed with the knowledge that coverage for those catastrophic illnesses that did not entail long-term care in nursing homes or home care programs could be provided cheaply and financed entirely through beneficiary premiums, Dr Bowen was able to see his cause through to legislative enactment in 1988. Once coverage for catastrophic expenses was on the table, however, it

From the United Hospital Fund of New York.
Reprint requests to Bruce C. Vladeck, PhD, President, United Hospital Fund of New York, 55 Fifth Ave, New York, NY 10003.

quickly became apparent that the major source of catastrophic health care expense among the elderly is indeed nursing home care and that much of the larger part of the issue remained unaddressed by the administration's proposal. Legislative proposals for long-term care coverage as part of the Medicare program soon surfaced, and while the enactment of any such proposal is not expected in the near future, awareness of the magnitude of long-term care expenses and of their often-catastrophic effect on the finances of elderly persons and their families is not likely soon to go away (Barry T. Crickman, "How To Handle Long-Term Health Care," *The New York Times,* January 18, 1988, p A19).

Third, and perhaps most straightforwardly, the introduction of the Medicare prospective-payment system educated many persons involved in health care to a basic reality that hospital discharge planners had known for years: Many elderly persons could appropriately be discharged from acute hospital care much more rapidly if the right sorts of facilities and services were available in their communities to receive them. In most communities, however, such facilities are not readily available in proportion to demand. The direct policy implications of this realization are, to date, less clear-cut than in the instances cited above, but it is now generally accepted that the prospective-payment system requires that deficiencies in the long-term care system must be addressed.[3]

For more than a decade, informed policy makers thought that better policy towards long-term care would involve both extremely difficult decisions and frightful expense, and thus they sought to avoid the issue. Now that other circumstances have conspired to make the issues unavoidable, it is far from clear how they will be resolved but increasingly clear that they must be.

The Demographic Dynamic

About 15% to 20% of persons aged 65 and older suffer chronic physical and cognitive impairment in their ability to conduct the normal activities of daily living of sufficient severity to require the assistance of others.[4(pp67-76)] With almost 30 million Americans in that age range, it means that between 4.5 and 6 million people need such regular assistance. Critical to understanding long-term care is recognizing that, while most of the assistance such persons need—with dressing, bathing, eating, financial and household management, and the like—is clearly not medical in content, the need for such assistance arises from medical problems. Another important fact is that, contrary to widespread public mythology, the overwhelming majority of elderly persons in need of continual assistance with activities of daily living receive it at home, in the community, from family members—overwhelmingly female family members, especially wives, daughters, and daughters-in-law—or, to a lesser extent, from friends and neighbors.[4(p150)] Only a quarter to a third of the disabled elderly receive formal, paid services, and at any one time most of this group are occupants of nursing homes.

The need for formal long-term care facilities arises in the first instance from the unprecedented demographic phenomenon of an aging population. That same phenomenon makes the continuing necessity for long-term care services not only inevitable but inevitably growing. For not only is functional impairment apparently an unavoidable concomitant of aging for at least some fraction of the population, its likelihood appears to increase monotonically, and sharply, with increasing age past 70 or 75. Thus, persons between 80 and 85 years are more than three times as likely to have impairments in activities of daily living as persons 60 to 70 years (Table 1).[5] Although the total proportion of the population that is 65 and older is not expected to increase dramatically for at least several decades, the elderly themselves are becoming increasingly old: while the number of persons older than 65 will increase by only 20% in the United States between now and the end of the century, for instance, the number of per-

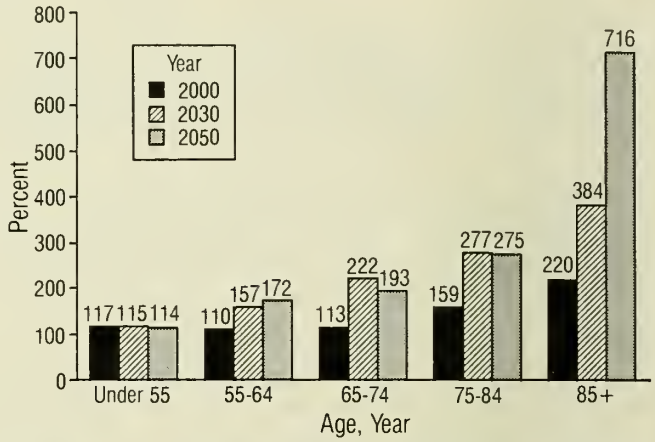

Figure 1.—The graph shows the projected growth in population, by age group, 1980 to 2050 (1980 = 100%). The bars represent projected population as a percent of the 1980 population (from Spencer[6]).

TABLE 1.—*Percent Distribution of Persons Aged 65 Years and Older By Number of Personal Care Activities That Are Difficult, According to Sex and Age, 1984**

	Number of Personal Care Activities That Are Difficult†					
Sex and Age, yr	*Total*	*None*	*1*	*2*	*3*	*4-7*
Both sexes			*Percent*			
65 and older	100.0	77.3	9.2	4.7	2.8	5.9
65-74	100.0	82.9	7.8	3.7	1.9	3.7
65-69	100.0	85.3	6.8	3.1	1.5	3.2
70-74	100.0	79.9	9.1	4.4	2.4	4.2
75-84	100.0	72.2	11.2	5.4	3.7	7.4
75-79	100.0	75.9	10.8	4.3	3.3	5.7
80-84	100.0	65.6	12.1	7.4	4.6	10.4
85 and older	100.0	51.2	12.8	10.2	6.7	19.2
Male						
65 and older	100.0	81.3	8.8	3.5	2.0	4.5
65-74	100.0	84.6	7.6	2.7	1.8	3.2
65-69	100.0	86.5	6.6	2.1	1.5	3.2
70-74	100.0	82.1	9.0	3.6	2.2	3.1
75-84	100.0	77.6	10.6	4.2	2.2	5.4
75-79	100.0	80.3	10.1	2.9	2.4	4.4
80-84	100.0	71.8	11.6	7.2	1.9	7.6
85 and older	100.0	60.1	13.2	8.3	3.5	14.9
Female						
65 and older	100.0	74.6	9.5	5.6	3.4	6.9
65-74	100.0	81.6	7.9	4.4	2.0	4.0
65-69	100.0	84.4	7.0	3.9	1.5	3.2
70-74	100.0	78.3	9.1	5.0	2.6	5.0
75-84	100.0	68.9	11.6	6.2	4.7	8.6
75-79	100.0	73.0	11.2	5.4	3.9	6.6
80-84	100.0	62.4	12.3	7.5	5.9	11.9
85 and older	100.0	47.2	12.6	11.1	8.1	21.1

*From Dawson et al.[5]
†Figures may not add to 100.0 because of rounding.

sons aged 85 and older is expected to increase by 65% (Figure 1).[6] Thus, even if no major changes are attempted in the organization of long-term care services, the long-term care system will undoubtedly change as a result of the increasing demographic pressures it will experience, just as it has changed over the past decade or so even in a time of policy and programmatic stasis.

Of all functionally impaired elderly persons, those most likely to use institutional services are those with the weakest family supports, the lowest incomes, and who are most socially isolated. Given the differential in life expectancy between the sexes, that means that persons admitted to nursing homes are predominantly women—mostly widows, divorcees, or women who have never married—in their late 70s and 80s, without substantial assets or income, a large proportion of whom have no surviving children or their children are themselves elderly, disabled, or distant geographically. Among elderly persons being maintained in the community, the clinical conditions most likely to precipitate entering an institution are incontinence and dementia, each of which imposes especially stressful burdens on caretakers.[7]

Nursing Homes

When support systems in the community are unavailable or are no longer able to maintain a person at home, nursing homes are the primary site for the institutional care of elderly persons; although the pathway of entry to the nursing home often runs through a general care hospital. More than 1 million elderly Americans a year are admitted to about 1.3 million nursing home beds; while the mean length of stay in nursing homes exceeds 18 months, the median is much closer to 100 days. Patterns of nursing home use appear to be dramatically bimodal. Many persons have relatively short nursing home stays. Some are discharged home after brief, essentially convalescent or habilitative, confinements. Some die relatively soon after admission or are readmitted to hospital for a terminal stay there. Many may experience the "revolving door" between hospital and nursing home. Still, on any given day, most nursing home residents are in the course of a long stay.[7]

Nursing home residents already have suffered considerable impairment on admission and become more impaired through the course of their stays. Only a decade ago, reports that as many as 25% to 40% of nursing home residents might not require even the minimal levels of care provided in many facilities were common. Today, while definitions of appropriateness and patterns of care have evolved, there is little question that in most communities, most nursing home residents are pretty ill and pretty disabled. Almost all have multiple, serious medical problems; perhaps as many as half have significant cognitive impairments.

Compared with other sorts of health facilities, nursing homes are both numerous and relatively small. The data are shockingly limited, but there are perhaps as many as 18,000 licensed nursing homes in the United States, operating between 1.25 and 1.5 million beds; the average facility thus still has fewer than 100 beds. Most nursing homes are privately owned, although increasingly by large, publicly traded corporations rather than the traditional "mom and pop" independent proprietors; approximately a quarter are operated by nonprofit organizations, most commonly affiliated with religious denominations; and about 10% of facilities—though with a much larger proportion of beds—are operated by government agencies, most commonly county governments.[6]

Compared with most other kinds of health facilities, nursing homes also generally provide only limited health services. Much of the dispute over the recently enacted revisions in federal regulatory standards centered on the proposal that all nursing homes employ at least one licensed nurse around the clock and at least one registered nurse on the day shift; though many facilities already far exceed those standards, somewhere between 10% and 20% of currently licensed facilities do not even meet them.[2(pp101-103)] Most hands-on care continues to be provided by aides and orderlies who, in many states before the passage of the new legislation, were not required to have any pre-employment training or other formal qualifications and who are generally employed at the minimum wage or close to it. Many nursing homes provide physical, occupational, and speech therapy, but only the large ones employ full-time staff in those departments. Administering prescription medications and providing therapeutic diets, in addition to minimal nursing care, are the only clinical services routinely provided by all nursing homes.

The provision of physician care in nursing homes is particularly problematic. Regulatory standards and common practice in most communities have assumed the applicability of the traditional hospital attending staff model to nursing homes, although reimbursement practices developed in response to billing abuses, along with various other pressures on most physicians, have long made that model inapplicable and irrelevant to most nursing homes. Thus, nursing homes are expected to have "organized medical staffs" and part-time medical directors, but each patient is also presumed to have his or her own attending physician. Most private practitioners visit nursing homes infrequently, if at all, so that the reality is that most nursing home residents receive little direct medical supervision. Nor is there any evidence that the increasing physician supply will sufficiently alter this pattern. When patients have acute medical problems that are not manageable by nursing care, standing orders, or a telephone consultation, nursing home residents are customarily shipped off to the nearest hospital, even if hospital admission is not medically required.[9(pp17-19)]

There are, of course, many elderly persons recuperating from an acute episode or slowly deteriorating from a chronic condition who do not require regular physician attention but need primarily to be cared for in a safe and supportive environment with some nursing care, assistance with activities of daily living, and regular professional nursing supervision. Many nursing homes serve the needs of such persons well. But it is far from clear that such a role for nursing homes is generally understood or accepted by patients and families, health professionals, or the people who make public policy about long-term care for the elderly. Precisely what it is that nursing homes are supposed to *do,* as opposed to what they actually do, has never been entirely clear.

The Fiscal Muddle

Nursing homes are both cheap and expensive. At an average cost of about $50 a day, including room, board, personal care, and some nursing, nursing homes house, feed, and care for elderly persons at a cost that is hard to imagine being much lower. On the other hand, an average nursing

home stay of 18 months thus costs $27,000 to $30,000, an amount that far exceeds the resources of most elderly persons and their families. In particular, because the persons most at risk for needing nursing home care are not average elderly persons but rather disproportionately poor and disproportionately very old, and because the need for nursing home care often culminates a series of medical incidents with substantial out-of-pocket and other costs, those most likely to need nursing homes are generally those least equipped to afford it.

Thus, of the approximately $30 billion now spent annually on nursing home care in the United States, nearly half comes from Medicaid, the federal-state program originally devised primarily to provide access to conventional medical care for the nonelderly poor.[10] Furthermore, while Medicaid pays only half of the system's total costs, its effect on the market for nursing home services is in fact still more complete and pervasive. Medicaid dominates nursing homes, just as nursing home expenditures increasingly dominate Medicaid.

The critical engine is the process of Medicaid eligibility. Medicaid coverage is available, regardless of medical needs, to any person whose income and assets fall below standards determined—at widely varying levels—by the states. But Medicaid coverage is also available, in most instances, to persons whose income or assets exceed the standard eligibility thresholds but who have medical expenses that, when subtracted from their total income, leave them below the standard. By far the most common instances of the latter route to eligibility involve protracted nursing home stays.

Typically, an elderly person with some cash assets (a life's savings) and a monthly income from Social Security slightly in excess of the poverty level—and thus substantially in excess of the Medicaid eligibility standard in most states—is admitted to a nursing home at monthly costs three or four times his or her monthly income. For some months, the nursing home bills are paid by drawing on the savings, but at some point the remaining assets fall below the Medicaid threshold, and Medicaid eligibility is established. Thenceforth, however long that person lives, as long as she or he remains in a nursing home or other health facility, Medicaid will pay the difference between the person's total income and the rate it allows the nursing home, plus an additional $25 or so a month (depending on the state) for "personal needs." Thus, while Medicaid is paying about half of total nursing home costs, because it is a secondary payer paying the net amount after the person's income, it is making those payments on behalf of perhaps two thirds of all nursing home residents at any given time. But most of the nursing home residents for whom Medicaid is paying became Medicaid recipients only after nursing home admission, a process over which Medicaid generally has little, if any, control.

By law, nursing homes (and other providers of health services) may not charge any other customer less than they are paid by Medicaid. As an expensive and politically sensitive public program, Medicaid in most states has generally taken advantage of its enormous market power vis-à-vis nursing homes by paying as little as it can get away with. Nursing home operators are thus especially eager to charge non-Medicaid patients as much as they can, but in so doing, of course, they accelerate the pace at which those residents "spend down" to Medicaid eligibility. Medicaid thus finds itself with more eligible applicants—a component of expense over which it has little control—and tends to respond by squeezing down where it does have control, on rates of payment to providers.

Notwithstanding the efforts of Medicaid administrators to limit payment levels to nursing homes, total expenditures for nursing home care under Medicaid have grown at a rate faster than that of both general price inflation and state revenues. Given the already minimal staffing levels of most nursing homes and the continuing inflation in other parts of the medical care market, in which nursing homes must compete for personnel and supplies, payment levels continue to increase. Most of those engaged in administering Medicaid funds have long since recognized that there is not much more to be cut from unit payments.

With only limited control of the eligibility process and payment levels, state governments have also sought to stem the tide of increasing nursing home expenditures by constraining the growth of supply—either directly, through certificate-of-need programs, or indirectly, through the manipulation of reimbursement practices, particularly as they affected capital costs of facility construction or acquisition. This effort to control supply has had a solid intellectual foundation. Many policy analysts, including this writer,[9(pp215-242)] recognized that a considerable number of nursing home residents were capable of being cared for in the community but that funds for community-based services were generally not available. We argued that a reorientation of the system would only be possible if the growth of nursing home supply were limited so that whatever incremental funds might be available were invested in home care. Thus, over time, demographic pressures would produce a better fit between the need for nursing home care and the supply of nursing home services.

To a considerable extent, at least in some states, this strategy has worked. In New York, for example, there are now more elderly, disabled Medicaid recipients receiving formal home care services than residing in nursing homes. Also, while starting from a much lower base than expenditures for nursing homes, home care services have been the fastest growing object of Medicaid expenditures over the past decade.[11] Whether those who have followed this strategy have persisted with it too long, given the inexorable growth of the population in need, or have slightly overshot the mark, is, however, another question. It is not clear, for example, whether the difficulties encountered in discharging patients from hospitals to appropriate facilities referred to earlier arise from problems in the placement process, aggregate supply shortages, or, more likely, both.

In short, from the viewpoint of state governments, long-term care, especially as it is provided in nursing homes, costs too much, is too often of marginal or inadequate quality, and there is not enough of it to go around. The federal government continues to pay its share of the Medicaid bill with even less control over the growth of expenditures—although the federal Office of Management and Budget continues to come up with schemes to transfer all the risks to the states.

Towards the Future

Given the seeming intractability of these problems and the current ideologic and political popularity of nongovernmental, "market" solutions to public policy problems, increasing attention has focused over the past several years on the development of private insurance mechanisms for long-term care. Arguing from the analogy of hospital care, propo-

nents of expanded private insurance for long-term care have contended that the problem of continual underfinancing of hospital care was resolved only once private insurance for hospital care expenses became widespread. These proponents then identified a number of barriers to the proliferation of private insurance for long-term care, ranging from regulatory restriction to consumer ignorance, and have urged policy interventions to remove these barriers. Those arguments have, in turn, fallen on receptive ears within the nursing home industry, which has long despaired of prospects for improved financing from the public sector, as well as within governmental agencies anxious to unload expected future liabilities. Programs to promote private long-term care insurance have thus recently been urged by study groups in both the executive and legislative branches of the federal government, as well as in several states.[12]

We should always be wary of such policy consensus, and indeed a recently completed study by the Brookings Institution torpedoes nearly conclusively the illusion of private long-term care insurance. Starting from the recognition that half the current financing of long-term care services is drawn from private resources, the Brookings researchers show that, even under the most favorable assumptions, private long-term care insurance is unlikely to ever reduce to any significant degree a reliance on public financing. Private insurance may well permit families essentially to prepay long-term care expenses and thus avoid the trauma of liquidating carefully saved assets at a time of particular stress, but it is unlikely to bring new private resources into long-term care of a magnitude sufficient to supplant public dollars. In other words, given the unavoidable basic costs of long-term care services, many families will simply never be capable of generating adequate resources to pay for needed services without impoverishing themselves earlier in life.[12]

If private insurance will not save us, what will? Is the future of long-term care really as gloomy as it appears to at least some analysts and commentators? The key to answering those questions, I propose, lies in a rethinking of some more basic issues about what long-term care facilities and services are supposed to do, and for whom.

In fact, we have never had consensus on the role long-term care services, especially nursing homes, are supposed to play in a system of care for the frail elderly. One of the reasons nursing homes are so often perceived as being unsatisfactory is that they are expected to do a number of different, contradictory things: relieve general hospitals, and those who pay for general hospital care, of elderly patients who still need inpatient bed care but who no longer require the full panoply of hospital technology; provide rehabilitative services to patients convalescing from specific illnesses such as strokes or hip fractures; provide a pleasant and humane environment in which very frail, socially isolated, but cognitively intact elderly people can live out their remaining years of life; and provide a caring and protected environment for severely demented people who may live for years with their impairments. Most nursing homes, expectably enough, are not financed, staffed, or organized to do all of these things with any degree of effectiveness, and, in the aggregate, there are probably not enough nursing home beds nor enough dollars in the long-term care system to do all of them well.

Once it is recognized, however, that the long-term care nonsystem does fulfill a number of different functions, it becomes possible to consider those functions separately and to explore mechanisms that might better serve each of them. Perhaps the easiest case involves the role of "safety valve" for the hospital system.

The original Medicare statute, which at least in that portion has never been substantively amended, provided a benefit of as long as 100 days of posthospital "extended care." That benefit was developed in part because Medicare was supposed to provide insurance for its beneficiaries for the services required by acute illnesses and the acute manifestations of chronic illnesses. Posthospital services, in contradistinction to real, at least partially custodial, long-term care services, obviously fit within that pattern of basic coverage.[13]

Medicare, it is now widely recognized, covers only a tiny fraction of nursing home care and only a slightly larger fraction of long-term care in-home services, but in so doing it is probably not adequately fulfilling its initial mandate and implicit commitment to its beneficiaries. That is even more the case to the extent that those now running the Medicaid system are attempting to economize on expenditures by drawing ever narrower the definition of an "appropriate" hospital admission. While it may not be appropriate from a purely technical point of view to retain people in acute-care hospital beds a moment longer than is necessary, it may well be appropriate, from a historical and clinical perspective, for Medicare to pay for whatever services follow immediately thereafter.

Indeed, there is increasing recognition of the need for "transitional care" for Medicare beneficiaries, which looks in most of its aspects much like the original statutory definition of extended care. Moreover, there is an abundance of capacity in those facilities that are the logical providers of such transitional or extended care: general hospitals. It is necessary to recognize, however, the extent to which extended care is a service fundamentally different from what is now generally defined as nursing home care, requiring fundamentally different patterns of organization, staffing, and financing.[14]

There are models. Perhaps the most relevant, if least obvious, are the extremely successful "swing bed" units operated, under existing law, in some small rural hospitals. The swing-bed program is not without its problems, but it would appear to contain the seeds of more rational future policy directions.[15] Similarly, there are individual models of both freestanding and hospital-based "nursing homes" that conform much more closely to an ideal of extended or transitional care than do conventional nursing homes. Such facilities tend to have lengths of stay that average around 30 days; discharge most of their patients back to the community; and employ significantly more physical and occupational therapists, as well as nurses, per bed than do conventional nursing homes. Care is paid for largely by Medicare.[16]

If we could begin to get an adequate policy towards extended care, to address what Brody has called "short-term long-term care," then more rational policies towards "long-term long-term care" should also be possible.[17] If Medicare starts living up to its end of the financing bargain, redefining federal, state, and private responsibilities for long-term long-term care becomes possible within the broader context of intergovernmental fiscal relationships. It should also become possible to address more effectively the substantial agenda of unfinished business on qualitative and service is-

sues for both nursing homes and home care once there is some greater clarity as to which patients each should be serving.

Among the questions that must be addressed to produce a more sensible long-term care policy are whether patients with Alzheimer's disease and other cognitive impairments should be cared for in the same facilities—as is now generally the case—as cognitively intact, extremely frail elderly people; whether the increasing severity and acuity of long-term care patients requires a concomitant reorientation and professionalism of nursing home staffing patterns; or whether the quality of life for nursing home residents might be improved by using such facilities only for those who are not seriously impaired. None of these questions have obvious a priori answers and none have yet been addressed in policy terms, but they must be resolved in one way or another if we are to extricate ourselves from the current muddle.

Given the unavoidable demographic realities, there is no question that, over time, long-term care will require more real resources, especially if further qualitative improvement comes to require still further real expenditures per unit of service. But the examples of other societies, as well as some clear thinking about our own, make apparent that a more effective and humane system that serves all those in need should be within our grasp, if we seek to grasp it.

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Health Care Delivery

Preventive Attitudes, Beliefs, and Practices of Physicians in Fee-for-Service and Health Maintenance Organization Settings

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To identify the self-reported differences in preventive practices, attitudes, and beliefs of physicians practicing in fee-for-service (FFS) and health maintenance organization (HMO) settings, we surveyed a 100% sample of primary care physicians practicing in a large, urban, closed-panel HMO and a random sample of physicians, in the same county, who were in an FFS practice. The FFS physicians were more likely to consider behavioral risk factors important than were HMO physicians, and they were more likely to ask their patients about behavioral risk factors. Fee-for-service physicians were more likely than HMO physicians to use continuing medical education courses to upgrade their skills in modifying behavioral risk factors. There was little difference in the self-reported proportion of patients with specific behavioral risks in the FFS and HMO practices. Also, both groups were comparable in their perception of their ability to do behavioral counseling and their perceived success in such counseling. We conclude that FFS physicians are more likely to have positive preventive beliefs, attitudes, and practices than are HMO physicians.

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Health promotion and disease prevention is an area where primary care physicians have the potential to decrease excess morbidity and mortality in their patient population. Previous studies have suggested that physicians believe that they have a responsibility to assist patients in modifying risk factors for disease.[1,2] There is also evidence that even modest interventions by physicians can have an effect on patients' behaviors and, while the percent of patients who modify their behavior in response to their physicians' advice may in some cases be modest, the absolute number of people who benefit from such risk reduction is substantial.[3]

Controversy exists about the extent to which the mode of payment of physicians influences preventive behaviors by those physicians. It is assumed that patients in prepaid practices (health maintenance organizations [HMOs]) are more likely to receive appropriate preventive interventions—as reimbursement is not an issue—than in fee-for-service (FFS) settings where prevention services frequently are not reimbursed. Conflicting evidence exists about whether or not this is the case.[4,5]

Two factors might seem to be confounding when examining the preventive services provided to patients in an HMO or an FFS practice. The first is the differential attraction of patients to a specific mode of practice. There is evidence that, in fact, HMOs do attract a different population from that using FFS.[6]

The second variable is a differential attraction of physicians to an HMO or FFS practice. It would be easy to speculate that preventive medicine-oriented primary care physicians might be differentially attracted to HMOs, as there is no concern for the reimbursement of preventive interventions. In fact, HMO physicians may be more inclined toward prevention, for if these interventions are successful, the HMO will be used less, resulting in more "profit" for the HMO. There are little or no data, however, that examine this hypothesis. For that reason, we undertook to examine the self-reported preventive beliefs, attitudes, and practices of primary care physicians in prepaid and fee-for-service practices.

Methods

In a survey of primary care physicians in HMO and FFS practices, we used a questionnaire that was a slightly modified form of a questionnaire that had previously been used to assess primary care physicians' preventive beliefs, attitudes, and practices.[1,2] It was mailed to all primary care physicians—family physicians, internists, and obstetricians—in a large, urban, closed-panel HMO. A total of 119 HMO physicians were identified initially, 6 of whom were ineligible to participate in the study as they had moved or died. We also mailed the questionnaire to a random sample of 249 FFS physicians practicing in the same county as those in the closed-panel HMO. A total of 20 fee-for-service physicians were ineligible for the study, as they had retired, died, or moved from the area.

Of the 113 eligible HMO physicians, 64, or 57%, returned a completed questionnaire. Of the 229 fee-for-service physicians, 104, or 45%, returned the questionnaire. The

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ABBREVIATIONS USED IN TEXT

CME = continuing medical education
FFS = fee-for-service
HMO = health maintenance organization

questionnaire had a series of questions designed to determine physicians' beliefs about behavioral risk factors for disease, their degree of success with modifying risk factors, the extent to which they inquired about risk factors, the extent of preparation to deal with patient behavior modification, their success rates, materials that might assist their efforts, and their desire for additional education in risk factor management.

Results

Responses to the questions were on a 4-point Likert scale. For the sake of analysis, the responses were dichotomized, with 1 and 2 being combined and 3 and 4 being combined. The results were analyzed by χ^2 with a Yates' continuity correction. When the difference examined was between two mean percentages, we used the t test. In addition, we used a nonparametric sign test on our data. This tests the null hypothesis that the distribution of differences between the groups is binomial, with $P = .50$. Thus, in response to a 24-item question, if the groups had similar opinions, we should observe 12 items higher for HMO physicians and 12 items higher for the FFS physicians.

Characteristics of the Respondents

Table 1 lists the specialties of our respondents in the HMO and FFS practices. The distribution was not significantly different. We used years since graduation from medical school as a proxy for age. The HMO physicians were younger, 17.1 mean years after graduation, than our FFS physicians, who were 25.3 years since graduation. This difference was statistically significant ($P \leq .001$). When we age-adjusted responses to the questionnaire items for the two groups, however, the statistical significance of no item was modified, so we used our unadjusted proportions.

The two groups differed in board certification, with 97% of the HMO physicians being board certified as opposed to 71% of the FFS physicians ($P \leq .001$). Because we had dichotomized our data and there were only two non-board-certified physicians in the HMO practice, any attempt to adjust for board certification introduced more bias than it removed.

There was no difference between the two groups in sex, percent of patients they referred, the percent of their patients who were referred to them, whether they graduated from a United States or a foreign medical school, or percent of time spent in direct patient care.

Fee-for-service physicians, as opposed to HMO physicians, identified a statistically smaller percentage of their total load as new patients, and they were more likely to report that a larger proportion of their patients were white, older than 65, and on Medicaid ($P \leq .05$).

Beliefs About Prevention

In both the HMO and FFS groups, all of the respondents (100% of both groups) thought that, in general, physicians should attempt to modify patients' behavioral risk factors.

The physicians were asked to respond to a series of risk factors and identify whether the risk factors were very important, somewhat important, somewhat unimportant, or very unimportant. Table 2 shows the proportion of those who rated the risk factors very or somewhat important, as opposed to the group as a whole. A number of items achieved statistical significance between the two groups, including three dietary items, three items relating to annual physical examinations or exercise tests, relaxation techniques, and the importance of sleep. In each of these the direction of difference was consistent, in that fee-for-service physicians were more inclined than HMO physicians to think the item was very or somewhat important. In 21 of the 24 items, the FFS physicians were more likely than HMO physicians to think the item was very or somewhat important. This difference, using our nonparametric sign test, was statistically significant ($P \leq .01$).

TABLE 1.—*Area of Specialty of Respondents**

	HMO		Fee-for-Service	
Specialty	*Number*	*Percent*	*Number*	*Percent*
General/family practice	38	59	46	48
Internal medicine	18	28	31	32
Obstetrics/gynecology	8	13	19	20
Total	64	100	96	100

HMO=health maintenance organization

*The fee-for-service respondents include 8 who did not indicate their area of specialization.

TABLE 2.—*Proportion of Those Physicians Who Felt the Risk Factor Was Very or Somewhat Important, By Mode of Practice*

	Practice Type	
Risk Factor	*HMO*	*Fee-for-Service*
Eliminate cigarette smoking	100	100
Eliminate pipe smoking	97	96
Eliminate cigar smoking	97	97
Drink alcohol moderately	86	92
Drink alcohol not at all	25	37
Limit daily caffeine intake	75	80
Eat breakfast daily	62	68
Avoid high cholesterol foods	94	93
Take vitamin supplements*	14	29
Minimize sugar intake†	44	68
Eat a balanced diet†	86	99
Avoid excessive calories	93	96
Avoid foods high in saturated fats	93	98
Decrease salt consumption	78	89
Be knowledgeable about drug contents	89	95
Have an annual physical‡	29	68
Have an annual exercise test‡	5	31
Have a baseline exercise test‡	11	55
Avoid unnecessary x-rays	70	74
Use protective equipment or work clothes if exposed to harmful substances	94	97
Engage in aerobic activities at least 3 times per week	92	80
Avoid undue stress	83	90
Regularly practice relaxation techniques‡	43	72
Always use a car seat belt	100	96
Get 7 hours of sleep a night‡	43	70

HMO=health maintenance organization

*Probability of differences between mode of practice ≤ .05.
†Probability of differences between mode of practice ≤ .01.
‡Probability of differences between mode of practice ≤ .001.

Preventive Practices

The physicians were asked the extent to which they gathered information about certain health behaviors. Table 3 shows the response of the two groups who always or regularly gathered the information, as opposed to those who occasionally, rarely, or never gathered the information. With the exception of four items, the FFS respondents were significantly more likely to indicate they gathered information about behavioral risk factors than were the HMO physicians. Even the four non-statistically significant items showed that FFS physicians were more likely to inquire about risk factors.

Preparation, Successes, and Support

Our respondents were asked how well prepared they were to counsel patients about various health behaviors, how successful they were in their efforts to achieve behavioral change, and how successful they would be given the appropriate support. There were no statistically significant differences between the HMO and the FFS respondents on these survey items. For each item, 80% to 90% of respondents thought they were very prepared or prepared to counsel patients. Between 40% and 70% of respondents thought they were very or somewhat successful in achieving behavioral change. Given the appropriate support, 80% to 95% thought they would be very or somewhat successful in achieving behavioral change.

TABLE 3.—*Proportion of Those Physicians Who Always or Regularly Inquired About Risk Factors, By Mode of Practice*

Risk Factor	Practice Type: HMO	Practice Type: Fee-for-Service
Smoking	91	95
Alcohol*	73	90
Other drugs†	71	87
Sugar intake‡	10	38
Diet for weight loss	46	55
Salt in the diet*	30	55
Other nutritional areas‡	13	40
Regular exercise	52	64
Stress‡	32	60
Family history of disease‡	68	91
Occupation	68	82

HMO=health maintenance organization

*Probability of differences between mode of practice ≤ .01.
†Probability of differences between mode of practice ≤ .05.
‡Probability of differences between mode of practice ≤ .001.

TABLE 4.—*Proportion of Those Physicians Very or Somewhat Likely to Take a Continuing Medical Education (CME) Course in a Subject Area, By Mode of Practice*

CME Course	Practice Type: HMO	Practice Type: Fee-for-Service
Communicative skills*	32	56
Behavior modification*	41	64
Smoking cessation†	40	59
Alcoholism and alcohol abuse*	34	56
Drug abuse*	32	57
Diet and nutrition*	43	67
Exercise and physical fitness*	46	69
Stress reduction*	46	73
Cancer risk reduction	57	63

HMO=health maintenance organization

*Probability of differences between mode of practice ≤ .01.
†Probability of differences between mode of practice ≤ .05.

Continuing Medical Education Needs

Respondents were asked how likely they would be to take a continuing medical education (CME) course on a variety of preventive topics if the course were available at a convenient time. Table 4 shows the proportion who were very or somewhat likely to take such a course if it were offered. In every subject area having to do with health behaviors except cancer risk reduction, more FFS respondents than HMO physicians indicated that they would be very or somewhat likely to take a CME course. Generally, the FFS physicians were as much as 20% more likely than the HMO physicians to take a health behavior CME course.

Types of Patients

We asked our respondents to estimate the proportion of their patients who had certain attributes, such as are overweight, smoke, or abuse alcohol or drugs. In only two categories were there any significant differences in their reported mean percent of patients with these attributes. The mean percent of the FFS physicians' patients who had problems of drug abuse was 7.3% as opposed to 4.5% of the HMO respondents ($P \leq .05$). By contrast, the HMO respondents had a mean percent of 53.9% sedentary patients in their practice as opposed to 45.5% of the FFS respondents ($P \leq .05$). In no other area did the physicians think that the mean percent of patients in their practice differed in their health behavior.

Person Responsible for Health Education

Respondents were asked who in their office is the major person responsible for health education. Table 5 shows the physicians' response to that item. In FFS practices, 94% of physicians said they were the major person responsible for health education. In HMOs, 67% of the physicians said they were the major source of health education. In the HMO group, 28% indicated that nurse practitioners had the major responsibility, as opposed to only 4% of FFS physicians who identified their nurse practitioner or physician's assistant as the primary person responsible for health education.

Adjuncts to Health Promotion Efforts

Respondents were asked the value of a variety of things that might assist them in their health promotion efforts.

TABLE 5.—*Person in Practice With the Major Responsibility for Health Education, By Mode of Practice*

Responsible Person	Practice Type: HMO, Number	HMO, Percent	Fee-for-Service, Number	Fee-for-Service, Percent
Physician	39	67	88	94
Nurse practitioner	16	28	1	1
Nurse	1	2	1	1
Physician assistant	0	0	3	3
Health educator	0	0	1	1
Nutritionist	1	2	0	0
Nurse midwife	1	2	0	0
Total	58	101*	94	100

HMO=health maintenance organization

*Error due to rounding.

These included such items as patient education material, physician education, referral information, financial reimbursement, and clear recommendations for health promotion or disease prevention. In only two items were there statistically significant differences between the HMO and the FFS physicians. Of the 11 items in this question, however, the FFS physicians were more likely than the HMO physicians on ten items to think that the items were very or somewhat valuable. Again, using the nonparametric sign test, this difference is statistically significant ($P \leq .01$).

Of the FFS physicians, 86% thought that physician education in behavioral modification was very or somewhat valuable, as opposed to 71% of the HMO physicians ($P \leq .05$). Of HMO physicians, 46% thought that financial reimbursement for time spent with patients for health promotion or disease prevention was very or somewhat valuable, as opposed to 85% of the FFS physicians ($P \leq .01$). For all the other items, 70% to 90% of both FFS and HMO physicians thought that the item would be very or somewhat valuable in their efforts. There was no significant difference between the 83% of HMO physicians and 88% of FFS physicians in response to the item, "more time for counseling and related health promotion activities."

Discussion

It appears the FFS physicians, as opposed to those in an HMO, have a stronger set of beliefs, attitudes, and positive practices related to health promotion and disease prevention. They are more likely than HMO physicians to think that some risk factors were more important than others. Some would criticize the FFS physicians because the items they were more likely than HMO physicians to think were very or somewhat more important are controversial preventive interventions, such as an annual physical examination, taking vitamin supplements, minimizing sugar intake, or practicing relaxation techniques for stress reduction. Noteworthy, however, is that in 21 of the 24 items that compose this question, the FFS physicians were more likely than the HMO physicians to think that the risk factors were very or somewhat important. This difference is statistically significant and bolsters our assertion that FFS physicians have stronger beliefs in preventive measures.

It appears that the FFS physicians routinely inquire about health behaviors more frequently than do HMO physicians. Unlike the information on risk factors, this is an area of substantially less controversy. Most physicians readily agree that a history should be taken about alcohol and drug use, diet, stress, or family history of disease.

Further, the FFS physicians show a strong commitment to disease prevention and health promotion in their attitudes toward continuing medical education in this area. This strong commitment is real, despite the fact that both FFS and HMO physicians feel well prepared to counsel patients. Moreover, a substantial portion of both FFS and HMO physicians feel very or somewhat successful in changing patient behavior, and there is no statistically significant difference between FFS and HMO physicians in their perceived success rate. Therefore, it appears that FFS physicians are more committed to health promotion and disease prevention, not more concerned with their ability to counsel or their perceived success rates.

Another possible explanation for the variation in beliefs, attitudes, and practices is the kinds of patients seen in FFS and HMO practices. If HMO patients were inherently less likely to have poor health behaviors than FFS patients, then the differences in beliefs and practices between the two groups might be appropriate because of the different nature of their patients. However, there are only two differences in the reported proportion of patients in the two groups with unhealthy behaviors. Fee-for-service physicians estimated that 7.3% of their patients have drug abuse problems as opposed to 4.5% of HMO physicians' patients, and HMO physicians report that 53.9% of their patients are sedentary, as opposed to 45.5% of FFS physicians' patients. There were no significant differences in the other 11 reported health behavior variables between the HMO and FFS physicians' patient panels.

Another possible explanation is the amount of time that an HMO physician may have for health promotion or disease prevention. Physician productivity is an important commodity in HMO practices. The press to see patients may affect a physician's ability to elicit more history about health behaviors or to expend time counseling patients. However, HMO and FFS physicians were not significantly different in their perception of the value of more time for counseling and health promotion activities—83% and 88%, respectively.

Another possible explanation is the availability of specialized health promotion personnel in an HMO. The HMO surveyed has available to its members a specialized health promotion and disease prevention program. In addition, a substantial number of the HMO physicians (28%) identified a nurse practitioner as the major person in their practice who is responsible for health education. Further, in asking our groups what would be useful adjuncts to assist their efforts, the FFS physicians were more likely to rate an adjunct such as a patient education handout as very or somewhat valuable. This is statistically significant and raises the question of what HMO physicians would find valuable to them in their efforts. It may be that they consider the availability of specialized health promotion personnel as valuable and may perceive modifying patients' behaviors as the domain of other specialties. We would note, however, that 100% of the HMO physicians answered that they should try to reduce unhealthy behaviors, even if they thought others should have primary responsibility.

A final point is that reimbursement for preventive services apparently could make a difference in health promotion activities by physicians. Only 46% of the HMO physicians, as opposed to 85% of the FFS physicians, thought that reimbursement for time spent doing health promotion or disease prevention was very or somewhat valuable. Given that the predominant form of physician reimbursement is still fee for service and that FFS physicians appear to be committed to health promotion and disease prevention, attention should be directed at mechanisms to facilitate the use of reimbursement for preventive services.

Our FFS physicians were more likely to be older and fewer of them were board certified. Both of these variables have been found to influence health promotion and disease prevention attitudes of physicians.[1] We were able to age-adjust our rates, and this adjustment did not significantly modify any of our findings. Unfortunately, given the small number of our respondents in an HMO practice who were not board certified, we could not adjust for board certification.

There are other methodologic weaknesses to this study. For example, it is based on physician self-reporting and not

on specific performance. In addition, it raises new research questions regarding the mode of practice and provision of preventive services. We encourage the continued exploration of the influence of the method of payment on the provision of health promotion and disease prevention services by physicians.

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Management of Heat Illness Syndromes

IN ATHLETIC COMPETITION, when the heat injury index approaches 20°C or 70°F, particular preventive measures—such as jersey changes or more water breaks—should be started, particularly for more susceptible persons. There are three heat illness syndromes: heat cramps, heat exhaustion or heat syncope, and heat stroke. One does not necessarily progress from one category to the next and may enter the scheme in the middle or at the very end.

Heat cramps occur mostly in the calf, thigh, abdomen, and the arms. They occur without injury and are caused by water or electrolyte loss or both. Treatment requires removal from the activity, gentle stretching, and replenishment of fluid.

Heat exhaustion or heat syncope results from an inadequate cardiovascular response to the stress of heat. One sees signs and symptoms related to an inadequate circulating blood volume. The presence of sweating does not rule out a heat-related illness. The treatment of heat exhaustion is to have the person lie down, elevate the lower extremities and replenish fluids . . . just as you would treat shock. Hypotonic solutions are helpful, but water by itself is most important. The core temperature remains normal.

Heat stroke is a medical emergency and carries a high mortality rate. These persons may show signs and symptoms similar to those of heat exhaustion. They become disoriented, irritable, aggressive, and emotionally labile. Taking rectal temperatures is a necessity in the management of heat illness syndromes. A reading of greater than 106° requires immediate cooling in an iced bath, or—second best—by fans blowing over wet sheets or towels. Intravenous fluid replacement should begin immediately, and the patient should be sent to hospital, since severe medical problems may develop, even after successful treatment.

Since long-term problems related to heat injury may be quite dangerous, prevention, of course, is the best course.

—MARTY IVEY, MD

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Health Manpower

Family Physicians for Underserved Areas
The Role of Residency Training

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Graduates of four rural and four urban family practice programs were interviewed to determine the nature of their practices and the factors that had influenced their practice location decisions. All programs gave residents substantial experience providing continuity of care for underserved populations. Of the 158 physicians surveyed, 58 (46%) were working in areas designated as underserved. The percentage of physicians in underserved areas was higher than that reported in other studies and was much higher than would be expected if practice sites were selected on the basis of population distribution alone. Notable differences in personal and practice characteristics were found between the physicians who chose to work in underserved areas and those who did not and between those who established practices in rural and in urban underserved areas.

(Gessert C, Blossom J, Sommers P, et al: Family physicians for underserved areas—The role of residency training. West J Med 1989 Feb; 150:226-230)

Since the mid 1960s, the number of physicians graduating from American medical schools has doubled and from 1970 to 1986 the number of physicians in practice increased from 326,000 to 525,000.[1] The physician-to-population ratio will increase from 152 per 100,000 in 1970 to 215 in 1990 and 240 by the year 2000.[2] Although many communities have an abundance of physicians, numerous remote rural and inner-city communities continue to be underserved.[3-7]

An important strategy for improving physician distribution has been to increase the number of physicians entering primary care specialties. This has been accomplished principally by providing support for primary care residency programs, by promoting primary care faculty development, and by supporting the development of family practice departments.[8]

Area health education centers (AHECs) operate with the goal of improving access to health care in underserved areas, using educational programs that are developed jointly by health professions training programs and representatives of underserved communities.[9] As part of their strategy for improving access to health care, the California AHECs have entered into partnerships with primary care residency programs. In many communities, the AHECs have selected family practice programs as partners because of their established commitment to care for underserved populations and their interest in developing clinical training experiences in underserved communities—with AHEC support.

The hypothesis underlying the California AHEC system's commitment to work with primary care residency programs was that many of the graduates of these programs would establish practices in underserved communities. We report on a study of the graduates of eight such family practice programs, with a focus on their work in underserved communities.

Subjects and Methods

Four urban and four rural family practice programs were selected for study. All met the following criteria:

- The goals of the program included preparing physicians for clinical practice in underserved areas.
- A major part of the residents' continuity of care training was in an underserved area, working with an underserved population, or both.
- At least 12 physicians graduated from the program between 1978 and 1981.

The four rural family practice programs were based at hospitals that averaged 250 beds (range, 176 to 417); the four urban programs were at hospitals that averaged 509 beds (range, 437 to 582) (Table 1).

The study subjects were those physicians who had completed their training from 1978 to 1981. As a result, the physicians generally had two to five years of practice experience by the spring of 1983 when the data were collected. A questionnaire was developed that included demographic and practice location decision questions that had been used in other studies.[10-12] Four interviewers were trained by one of the authors (M.D.C.). About two thirds of the interviews were done in person, the rest by telephone.

The census tract numbers for the physicians' practice locations were identified by using zip code maps and 1980 census map overlays. Census data were recorded on the eth-

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ABBREVIATIONS USED IN TEXT

AHEC = area health education centers
CHMPC = California Health Manpower Policy Commission

nicity, poverty level, population, and population density of each physician's practice community.

The medical service study area, as defined by the California Office of Statewide Health Planning and Development, was used as the geographic unit of analysis. Medical service study areas are aggregations of census tracts and may represent an entire rural county or a small portion of a densely populated urban area. The Office of Statewide Planning and Development and the California Health Manpower Policy Commission (CHMPC) define a medical service study area as rural if it "has a population of fewer than 250 persons per square mile and . . . no town . . . with a population in excess of 20,000." The CHMPC criteria for designating an area as medically underserved is "a medical service study area with a ratio of population to each primary care physician equal to or greater than 1,967 to 1 primary care physician."[13] This commission also recognizes ratios of 1,855 persons to 1 primary care physician for designating some medical service study areas that meet additional special criteria.

The CHMPC population and population density criteria were also applied to the practice locations of physicians not in California, and information from the appropriate state health department was used to determine whether practice locations met the same criteria.

Results

All 173 of the 1978 to 1981 graduates were located, and 158 (91%) were interviewed during the three-month study period (Table 2). Of these, 126 were clinically active family practitioners in California.

Almost half (46%) of the California physicians were practicing in underserved areas, as defined by the CHMPC (Table 3). Of the California physicians, 81% were in urban areas and 19% were in rural communities. Of the graduates who had remained in California, 64% (80 of 126) were practicing in the same county in which they had completed their training.

Physicians' Backgrounds

The California physicians (n = 126) included a large number of nonwhite minorities (n = 32, 25%) and women (n = 31, 25%). In comparing the physicians practicing in underserved areas (n = 58) with those in better-served communities (n = 68), no significant differences in ethnicity were found, nor were any significant differences noted in age, sex, marital status, or number of children. In fact, the only demographic difference between the physicians working in underserved areas and those in better-served areas was that more physicians in underserved areas had spouses who attended rural high schools (38% versus 18%).

Comparing physicians in urban underserved areas with those in rural underserved areas revealed several significant differences. More minority physicians had developed practices in urban areas; in fact, half (16 of 32) of all of the minority physicians in the study had established practices in urban underserved areas. When compared with those in urban underserved areas, the physicians in rural underserved areas had larger families (1.6 versus 0.9 children) and more frequently had spouses with a rural background (89% versus 16%).

Social, Community, and Professional Factors

The physicians were asked which various factors had influenced their selection of practice locations (Table 4). "Opportunity to practice in a salaried position" and "ability to practice with a nurse practitioner or physician assistant" were valued more highly by physicians in the underserved areas than by those in better-served areas. Also, physicians in underserved areas placed relatively less importance on "access to medical consultation," "proximity of extended family and friends," and "quality of community services (police, fire, schools)."

The physicians in rural underserved areas were more likely to consider "size of community" and "amount of crime" in making their practice location decisions, while urban physicians placed more importance on "availability of high quality continuing medical education," "economic condition of the community," "nearness of academic medical center," and "proximity of extended family and friends."

Practice Characteristics

Practice characteristics of physicians in underserved areas (n = 58) were compared with those of physicians in better-served areas (n = 68), and comparisons were made between the practices in urban (n = 42) and rural (n = 16) underserved areas. Physicians in underserved areas more frequently identified publicly funded clinics and emergency departments as their primary practice locations (Table 5); private practice and prepaid group settings were more frequently cited by physicians in better-served areas. There was greater use of Medicaid (Medi-Cal) by patients in under-

TABLE 1.—*Participating Hospitals*

Hospital Program	*Rural Hospitals (n=4)*	*Urban Hospitals (n=4)*
Bed Size		
Average	250	509
Range	176 to 417	437 to 582
Residency graduates		
Total (1978 to 1981)	101	72
Average per program	25	18
Range per program	17 to 37	12 to 24
Number interviewed	95	63

TABLE 2.—*Practice Locations*

Demographics of Graduates	*Total Eight Programs* No.	% *
Number Interviewed	158	100
Practice Locations		
Rural	41	26
Urban	112	71
No practice location†	5	3
State of Residence		
California	126	80
Other state	28	18
Out of USA	2	1
No permanent residence	2	1

*All percentages have been rounded to equal 100%.
†Two physicians were practicing out of the United States, one physician was in postgraduate training, one physician was working as a nonclinical consultant, and one physician was not in medical practice.

TABLE 3.—*Practice Locations of 126 Family Physicians in California*

Practice Location	Urban No.	Urban %*	Rural No.	Rural %*	Total No.	Total %*
In state-designated underserved area†	42	33	16	13	58	46
Not in designated area	60	48	8	6	68	54
Total	102	81	24	19	126	100

*All percentages have been rounded to total 100%.
†As defined by the California Health Manpower Policy Commission.

TABLE 4.—*Social, Community, and Professional Factors Influencing Practice Location Selection**†

Influential Factor	Total, n=126	Not in Underserved Areas, n=68	In Underserved Areas, n=58	In Urban Underserved Areas, n=42	In Rural Underserved Areas, n=16
A feeling of being needed	66	57	75	73	81
Acceptance of family practice by community	71	74	68	61	88
Size of community	66	71	61	54‡	81‡
Opportunity to practice in a salaried position	48	38‡	60‡	61	56
Access to medical consultation	63	73‡	51‡	54	44
Availability of high quality continuing medical education	50	50	51	58‡	31‡
Economic condition of community	53	54	51	58‡	31‡
Part-time teaching opportunity	39	34	46	51	31
Ability to practice with nurse practitioner or physicians' assistants	29	18‡	42‡	37	56
Children's educational needs or opportunities	42	47	37	29	56
Nearness of academic medical center	40	43	37	42‡	25‡
Proximity of extended family and friends	48	57‡	37‡	39	31
Employment or educational opportunities for spouse	45	53	35	37	31
Amount of crime	41	48	32	22‡	56‡
Quality of community services (police, fire, schools)	33	47‡	16‡	12	25
Previous commitment to serve a medically underserved population: NHSC, military, or other obligation	4	0‡	9‡	12	0

NHSC=National Health Resources Corps

*The numbers represent percentage of respondents indicating that factor was positive.
†Original 5-point rating scale (1=strongly negative to 5=strongly positive) was condensed to three responses—negative, neutral, and positive; χ^2 statistical tests were done, and the significance level was set at $P \leq .05$.
‡Significant at $P \leq .05$.

served areas, but no significant differences between the urban and rural subsamples were noted. In fact, no significant differences in practice arrangements or payment methods were identified between the physicians in the urban and rural underserved areas. Overall, the work weeks of physicians in underserved areas were similar to those in better-served communities, but the physicians in rural underserved areas worked more hours (60.8 versus 49.5) and had almost twice as many inpatient or emergency department contacts as did physicians in urban underserved areas. Physicians in underserved areas also spent more time each week teaching (5.3 versus 2.2 hours).

Discussion

The factors that influence the geographic distribution of physicians have been studied extensively in the past 20 years.[7,14-16] The location of medical education—both undergraduate and graduate—is clearly the most important determinant of eventual practice site selection.[17,18] This is confirmed by our finding that 64% of the study physicians were practicing in the same county where they had completed their training.

Although the demonstrated relationship between site of residency training and eventual practice location provides health planners and policymakers with a powerful tool, getting residents to stay near where they are trained provides only a partial response to the problem of physician maldistribution. It is even more important to develop programs that encourage physicians to work in underserved communities after completing training. The finding that 46% of physicians in California had established practices in state-designated underserved areas is remarkable in light of the social forces contributing to physician maldistribution and evidence that most physicians continue to locate in high physician density areas.[3,5,6] By comparison, in the only other published study using the same criteria of the California Office of Statewide Health Planning and Development for designating underserved areas, 31% of the graduates of six California family practice programs had entered practice in underserved areas.[19] Moreover, these data show that only 25% of California's population live in state-designated underserved areas. Therefore, the finding that 46% of the study physicians were practicing in underserved areas is much higher than would be expected if these physicians were distributed according to population alone.

We think that the practice location decisions of the physicians in this study were strongly influenced by the nature of their residency programs. The goals included a commitment to improving the distribution of physicians, and each program provided residents with substantial continuity of care experiences with underserved populations. The content—as well as the location—of these programs increased the willingness of these young physicians to locate in underserved areas. If primary care physicians are to gain the skills and

TABLE 5.—*Practice Characteristics of Family Physicians in California**†

Primary Practice Setting	Total, n=126		Not in Underserved Areas, n=68		In Underserved Areas, n=58		In Urban Underserved Areas, n=42		In Rural Underserved Areas, n=16	
	No.	%	No.	%	No.	%	No.	%	No.	%
Private practice, solo	32	25	19‡	28	13‡	22	9	21	4	25
Private practice, group	37	29	26‡	38	11‡	19	7	17	4	25
Prepaid group	12	10	9‡	13	3‡	5	2	5	1	6
Emergency department (noncontinuity-of-care facility)	12	10	5‡	7	7‡	12	4	10	3	19
Publicly funded clinic	32	25	8‡	12	24‡	41	20	48	4	25
Unknown	1	1	1‡	2	0‡	0	0	0	0	0

*The numbers represent percentages and may total more or less than 100% due to rounding.
†Statistical significance tested by using χ^2 ; $P \leq .05$.
‡$P \leq .05$.

confidence necessary to establish their practices in underserved areas, they must be given extensive experience providing high-quality continuity of care to underserved populations.

Other studies of physician distribution, and particularly family practice follow-up studies, have not distinguished between urban and rural underserved areas; in many cases they have not addressed inner-city areas at all. In part, this is because of the absence of an appropriate unit of analysis, in that the standard metropolitan statistical area—the most widely cited geographic unit—does not distinguish between urban subareas that are in need of services and those that are not.

The use of "rural" as a proxy for "underserved" in physician distribution studies has assured that the only socially desirable benefit of physician redistribution that has been measured has been the increase in the number of physicians working in small or remote rural areas. This approach has tended to ignore the fact that while both remote rural communities and inner-city communities have been unattractive to physicians, this has been for different reasons.

Previously published studies on practice location have shown that physicians who choose urban areas tend to value professional factors, while rural physicians place more importance on personal and family aspects of their communities.[14,20] Our findings suggest that the decision to locate in an urban or rural community is largely independent of the decision of whether to work in an underserved area. Physicians who choose urban areas share a common set of values, regardless of whether they are choosing to work in an underserved area or not; the same is true of physicians who choose rural areas. For example, we found that physicians in rural underserved areas have more rural family ties and larger families; this is consistent with other studies of how all rural physicians select their practice locations.[15]

On the other hand, we found that physicians in underserved areas—urban or rural—tended to share several characteristics. Such physicians more frequently chose salaried positions and opportunities to work with mid-level practitioners than physicians in better-served areas. Physicians in underserved areas placed less importance on "access to medical consultation," "proximity to extended family and friends," and "quality of community services." These findings are consistent with those of the few published studies of physicians who choose to work with underserved populations.[21]

It is well established that minority physicians tend to serve minority communities.[22] We found that half (16 of 32) of the minority physicians in our study had established practices in urban underserved areas. Our study included a higher percentage of minorities (25%) than had been reported in two previous surveys,[10] and minorities were slightly overrepresented among the physicians in underserved areas. The high percentage of women (25%) did not appear to contribute to the results, in that the women were distributed no differently than their male colleagues.

This study did not provide data on the role of indebtedness in the distribution of physicians. The limits of supply-and-demand forces in meeting the needs of underserved communities are well documented.[3,6,7] On balance, economic forces may actually have a negative effect on specialty and geographic distribution in this era of increasing student indebtedness and narrowing marketplace opportunities.[2] Clearly, financial considerations prevent some people from going to medical school at all and discourage many physicians from entering practice in underserved areas. These forces operate apart from physicians' personal or social goals and their training.[1]

The practices of physicians in underserved areas differed from those of physicians in better-served communities in several respects. For example, only 41% of physicians in underserved areas were in solo or group private practice, compared with 66% of the physicians in the better-served areas and 74% to 87% in published studies.[11,16,23] Of physicians in underserved areas, 41% reported "a publicly funded clinic" as their primary practice site, compared with 12% of physicians in better-served areas.

The physicians in rural underserved areas worked approximately ten hours a week more than physicians in urban underserved or better-served communities. Most of this incremental time difference was spent doing inpatient and emergency department care. Whether this influenced the choice of practice location could not be determined from our data. In a comparable study of graduates of New York state family practice programs,[12] more hours of work a week were recorded (72.1 versus 52.4), but the New York group reported a lower percentage of time in clinical activity (64.6% versus 81.7%). In the aggregate, while physicians in underserved areas did not work more hours than physicians in better-served areas, physicians in rural areas (regardless of whether or not the areas were underserved) did work longer hours than their urban counterparts. This information should be of substantial interest to physicians in their career planning.

Our findings and the published differences in factors used by physicians to select urban and rural practice locations[14,20]

should help directors of urban and rural programs to recruit, select, and train physicians to meet the specific needs of their respective communities.

Summary

All 1978 to 1981 graduates (173) of eight California family practice programs were located, and 91% (158) were interviewed. A total of 126 had remained in California, and 46% of these had established practices in areas designated by the state as underserved. This high percentage of graduates in underserved areas related in large part to the fact that the programs selected for study had a strong commitment to placing graduates in underserved areas. This commitment was expressed in their providing continuity of care training experiences with underserved populations.

Our findings suggest a successful formula for placing physicians in underserved areas:

- Primary care residency training programs should be developed and supported in areas that are within or adjacent to underserved areas.
- Residents should be selected on the basis of those aspects of their backgrounds and expressed values that tend to be predictive of their likely preference for an urban or rural practice setting, depending on the location and goals of the residency program.
- Most importantly, residency programs should assure that each trainee is provided with substantial continuity of care experience working with underserved populations.

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☐ ACP Associate, Member (graduated 1983 and later) . . $120
☐ Nonmember $300
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US $ Total Enclosed . . . . . _____

(*Letter of verification must accompany form)

SPECIALTY (please check only ONE)

☐ (01) Allergy/Immunology
☐ (10) Cardiovascular Disease
☐ (12) Clinical Pharmacology
☐ (14) Dermatology
☐ (17) Endocrinology/Metabolism
☐ (19) Gastroenterology
☐ (22) Hematology/Oncology
☐ (25) Infectious Diseases
☐ (27) General Internal Medicine
☐ (31) Neurology
☐ (48) Pulmonary Disease
☐ (51) Nephrology
☐ (54) Rheumatology
☐ (99) Other_____

For information contact:
American College of Physicians
1-800-523-1546, extension 1229
(in Pennsylvania, 215-243-1200, extension 1229)

CONTINUING MEDICAL EDUCATION

(Continued from Page 154)

February 20-22—**Clinical Hematology and Oncology: 1989.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, Conference Coordinator. (619) 457-8556.

March 8-9—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square. Wed-Thurs. 14 hrs. $250. Contact: UCSF.

March 17-19—**Gastroenterology Update Cruise.** Center for Health Education at Queen Mary Hotel, Long Beach. Fri-Sun. Contact: Center for Health Education, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

March 17-23—**Internal Medicine 1989: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Fri-Thurs. 54 hrs. $495. Contact: Jacqueline Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 21-24—**Topics in Rheumatology II.** Straub Foundation at Ilikai Hotel, Honolulu, Hawaii. Tues-Fri. 16 hrs. $350. Contact: Juliana J. Woo, MPH, Straub Foundation, 846 S Hotel St, #302, Honolulu, HI 96813. (808) 524-6755.

April 6-7—**Diseases of the Urinary Tract.** Stanford Division of Urology at Hyatt Rickeys Hotel, Palo Alto. Thurs-Fri. 15 hrs. $300. Contact: STAN.

April 8—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. $120. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 14-15—**National Melanoma Conference.** Northern California Cancer Center and Melanoma Foundation at Sir Francis Drake Hotel, San Francisco. Fri-Sat. 9.25 hrs. $225. Contact: Chris Wagner, (415) 595-2704.

May 6-13—**Internal Medicine.** STAN at Mauna Kea Beach Hotel, Hawaii. Sun-Fri. 25 hrs. $540. Contact: STAN.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 14-16—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt Union Square. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

OB/GYN

March 10—**Contemporary Concepts in Reproductive Health Care: 1989.** Planned Parenthood/Alameda-San Francisco and UCSF at Merrit Peralta Health Education Center, Oakland. Fri. Contact: Marsha Gelt. (415) 441-7858.

March 15-18—**Horizons in Reproductive Health.** UCSD and Planned Parenthood/San Diego at Hotel del Coronado, San Diego. Wed-Sat. 15 hrs. $350. Contact: Carolyn Ferrer, Conference Coordinator, (619) 231-6760.

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

July 10-12—**Breastfeeding: A Natural World Resource.** La Leche League International at The Anaheim Hilton and Towers. Mon-Wed. 16 hrs. Contact: c/o La Leche League International, 9616 Minneapolis Ave, Franklin Park, IL 60131. (312) 455-7730.

OPHTHALMOLOGY

April 1—**Visions in Ophthalmology '89.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Sat. 5 hrs. $100. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

PEDIATRICS

February 15—**27th Annual Parmelee Memorial Lecture: Symposium on Current Advances and Ethical Considerations in Perinatal Medicine.** Los Angeles Pediatric Society at University Hilton Hotel, Los Angeles. Wed. 6 hrs. $50. Contact: Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 18—**Management of Obstructive Airway Disease in Children: Interaction of the Pediatrician and Surgeon.** Los Angeles Pediatric Society at LAC-USC Medical Center. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 18—**Management of Congenital Urologic Prohlems in Children.** Los Angeles Pediatric Society at LAC-USC Medical Center. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 18—**Management of Pediatric Urologic Emergencies and New Techniques for Hypospadias.** Los Angeles Pediatric Society at LAC-USC Medical Center. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

February 20-22—**Pediatrics Update: 1989.** UCD at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 24-25—**California Conference on Health Care for Foster Children.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 14 hrs. $125. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 9-10—**Child Abuse and Neglect.** UCD at Sacramento Inn. Thurs-Fri. 11 hrs. $150. Contact: UCD.

March 9-11—**Brain Insults in Infants and Children: Diagnosis and Modern Management.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thurs-Sat. 15 hrs. $325. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 17-18—**Hematology and AIDS: Neonatal & Pediatric Perspectives II.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 12 hrs. $160. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 30-April 1—**Pediatric Trends.** American Academy of Pediatrics at Waiohai Hotel, Kauai, Hawaii. Thurs-Sat. 16 hrs. Contact: CME Registration, Department of Education, AAP, PO Box 927, Elk Grove Village, IL 60009-5005. (800) 433-9016.

April 14-16—**2nd Annual Pediatrics in Progress.** American Academy of Pediatrics at Las Vegas. Fri-Sun. 18 hrs. Contact: American Academy of Pediatrics, Dept of Education, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016 ext 7657.

April 15—**New Information on Old Exanthems.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Immunizations: Current and Future Vaccines.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Menstrual Problems in Adolescents.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Common Presentations of Uncommon Conditions; Uncommon Presentations of Common Conditions.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Atherosclerosis; Pathogenesis and Screening.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Hypertension in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Office Evaluation of Sports Injuries.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Fitness Training in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

(Continued on Page 237)

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For respiratory tract infections due to susceptible strains of indicated organisms.

Summary.
Consult the package literature for prescribing information.

Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.
Administer cautiously to allergic patients.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever): 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

[061088L]

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CONTINUING MEDICAL EDUCATION

(Continued from Page 234)

RADIOLOGY

February 23-25—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Rancho Mirage. Thurs-Sat. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

February 24-26—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel Rancho Mirage, Palm Springs. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, Ryals & Associates, (404) 641-9773.

March 5-9—**Thoracic Imaging '89.** Society of Thoracic Radiology at Hotel Del Coronado, San Diego. Sun-Thurs. 32 hrs. $400. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

March 10-12—**Musculoskeletal Imaging: The State of the Art.** Hoag Memorial Hospital at Four Seasons Hotel, Newport Beach. Fri-Sun. 16 hrs. $375. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 16-21—**9th Annual San Diego Residents Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 28-30—**14th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

May 2-6—**9th Annual Mid-Pacific Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Royal Waikoloan Hotel, The Big Island of Hawaii. Tues-Sat. 19 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078

SURGERY

January-July—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 9-11—**Knee Reconstruction Surgery: ACL Repair, Patella Alignment and Total Knee Replacement.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Thurs-Sat. 30 hrs. Contact: Bonny Mower, Conference Coordinator, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 15-17—**Perioperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. $350. Contact: UCSF.

March 16-19—**Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 6-8—**Postgraduate Course in General Surgery.** UCSF at San Francisco Hilton. Thurs-Sat. Contact: UCSF.

May 6-13—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Hawaii. Sun-Fri. 25 hrs. $450. Contact: STAN.

May 20—**6th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic Surgery Medical Group at La Jolla Marriott Hotel. Mon. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

OF INTEREST TO ALL PHYSICIANS

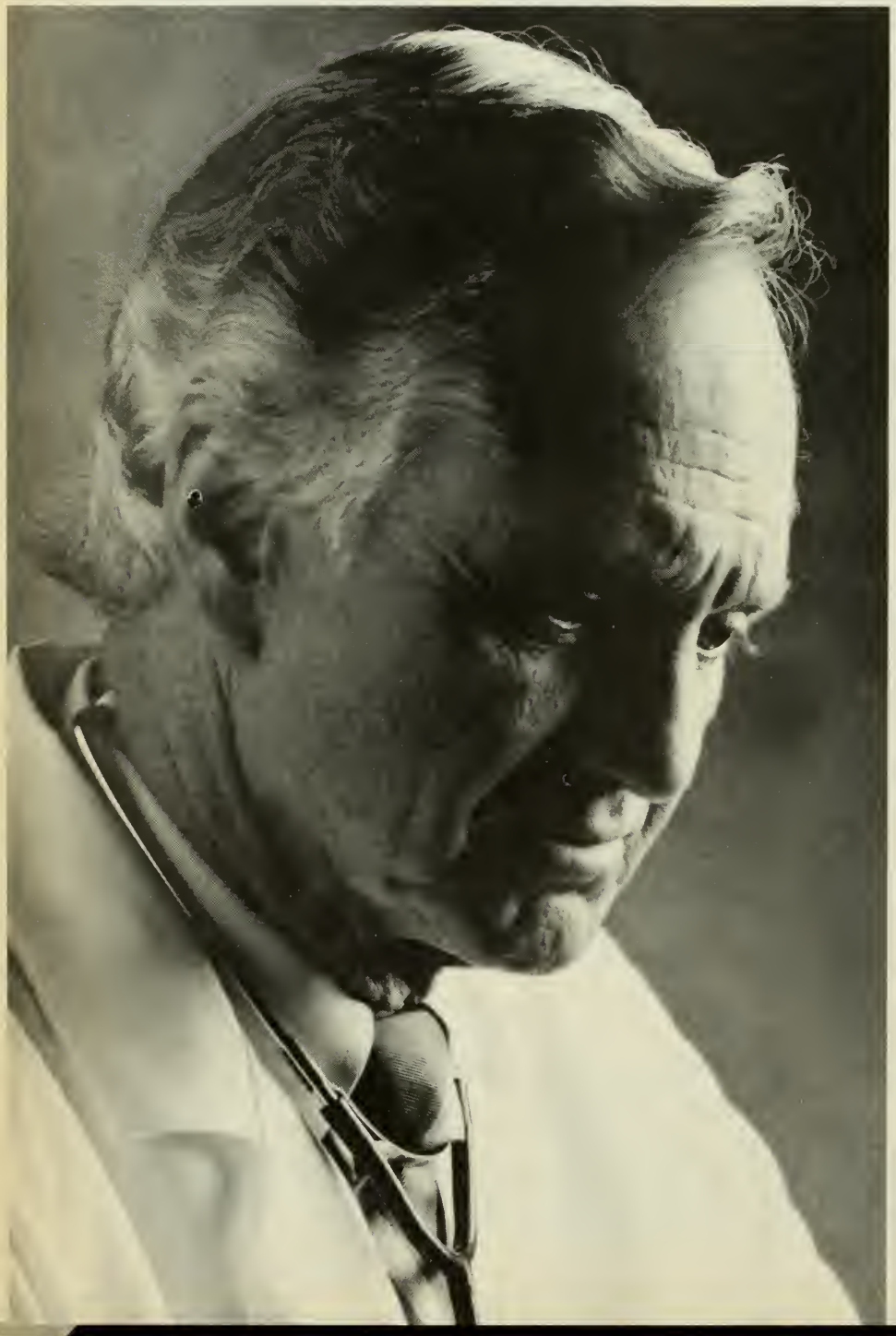
February 7-April 25—**Common Problems in Primary Care: 15th Annual Review.** USC. 2 weeks. 33 hrs. $410. Contact: USC.

February 13-17—**Occupational Respiratory Protection.** USC. 3.5 hrs. Contact: USC. (213) 743-6523.

February 15-18—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 240)

No Need to Feel Helpless...



Few things elicit feelings of depression, rage, helplessness and exasperation as thoroughly as receiving suit papers for a malpractice claim. This physician suffered just such an unpleasant experience... but his odds of winning were better than most. Why? Because his professional liability insurance carrier is Insurance Corporation of America.

The circumstances of this claim could occur and have occurred in operating rooms and doctors' offices everywhere. A routine surgical procedure went sour when, for no apparent reason, the patient suffered a cardiac arrest. Prompt and proper attempts at resuscitation failed. Our physician was sued along with other

surgeons in the operating room, the primary care physician, the anesthesiologist and the hospital.

Subsequent to surgery, it was determined the patient had arrested as a result of an allergic reaction to the anesthesia. Unlike other carriers involved, who settled quickly to avoid costly "death incident" litigation, ICA recognized our physician was not at fault. Fortunately for him, ICA is dedicated to the strongest claims defense possible. And because ICA also understands that a doctor's most valuable asset is his reputation, protecting it becomes *our* bottom line.

So ICA and the doctor fought alone — and at ICA's expense. ICA in-house attorneys screened and selected local defense attorneys skilled in malpractice cases and familiar with the judicial climate of the region. Then, they planned strategy, investigated the facts, and monitored the defense.

During discovery, information was released indicating the patient had previously undergone similar surgery under anesthesia *without* incident. Because of ICA's diligence and our willingness to exhaust all legal remedies, the jury was allowed to hear the autopsy report as well as the patient's past medical history. Those defendants who settled quickly never had an opportunity to present that evidence. And ultimately our insured was exonerated.

What does this mean to the doctor? He leaves the courtroom with his reputation, his policy limits and his checkbook intact, all because of his partnership with ICA, where we put reputation, principles and dignity ahead of the quick fix. The reason why? Because ICA is people who *care*. Period.

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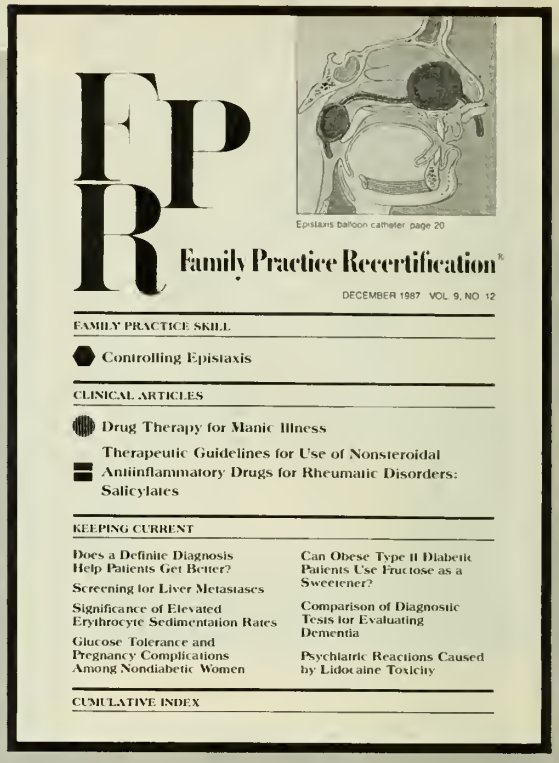
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CONTINUING MEDICAL EDUCATION

(Continued from Page 237)

February 16-18—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and the Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

February 17-18—**A National Conference on Ethical Issues in the Care of Individuals with Handicapping Conditions.** North Bay Regional Center at Red Lion Inn, Rohnert Park. Fri-Sat. 10 hrs. Contact: Ethical Issues Conference, North Bay Regional Center, 1710 Soscol Ave, Napa 94559-0444. (707) 252-0444.

February 17-18—**Practical Review and Update of Infectious Disease.** UCD at Hilton Inn, Sacramento. Fri-Sat. 11 hrs. $155. Contact: UCD.

February 20-22—**9th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Perspective on Alcoholism Treatment: Ongoing Issues in Integrating the 12-Step Program.** Annenberg Center at Betty Ford Center at Eisenhower, Rancho Mirage. 13 hrs. Contact: Annenberg Center, Eisenhower Medical Center, 39000 Bob Hope Dr, Rancho Mirage 92270-3298. (800) 621-7322.

February 23-24—**Transportation of Hazardous Materials/Waste.** USC. 1.4 hrs. Contact: USC. (213) 743-6523.

February 24-March 1—**57th Annual Postgraduate Convention.** Loma Linda Alumni Association at Loma Linda. Fri-Wed. 32 hrs. Contact: Alumni Association, School of Medicine, Loma Linda University, 11245 Anderson St, Loma Linda 92354. (714) 824-4633.

February 25-March 4—**Update: Controversies in Emergency and Primary Care.** Scripps Memorial Hospital Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 27-28—**Back Injury Prevention.** USC. 1.4 hrs. Contact: USC. (213) 743-6523.

February 27-March 2—**Post Concussion Syndrome: Advances, Update and Review.** Centre for Neuro Skills and Southern California Neuropsychiatric Institute at Caesar's Palace, Las Vegas, Nevada. Mon-Thurs. 21 hrs. Contact: Sherry Ryan, SCNPI, La Jolla Blvd, La Jolla 92037. (619) 454-2102.

March 2-3—**Vitamins and Cancer Prevention.** UCLA at Neuropsychiatric Institute, Los Angeles. Thurs-Fri. $68. Contact: UCLA.

March 3-5—**Asia Pacific Alzheimer's Disease Conference.** Pacific Islands Geriatric Education Center at Hilton Hawaiian Village, Honolulu, Hawaii. Fri-Sun. 21 hrs. $300. Contact: Katherine Kim, Pacific Islands Geriatric Education Center, 347 N Kuakini St, Honolulu, HI 96817. (808) 523-8461.

March 3-5—**10th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Hyatt Regency, San Francisco. Wed-Fri. $365. Contact: UCSF.

March 4-5—**26th Annual Clinical Hypnosis Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Sat-Sun. 28 hrs. $350. Contact: Jan Brooks, 615-27th St, San Francisco 94131. (415) 826-0533.

March 5-8—**Asia-Pacific Osteoporosis Conference.** Kuakini Osteoporosis Center at Hilton Hawaiian Village, Honolulu, HI. Sun-Wed. 25 hrs. $450. Contact: Shirley Kuma, KOC, 347 N Kuakini St, Honolulu, HI 96817. (808) 547-9578.

March 8—**Veterinary Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

March 8-10—**9th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF Department of Radiation Oncology at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF. (415) 595-2704.

(Continued on Page 241)

CONTINUING MEDICAL EDUCATION

(Continued from Page 240)

March 10-11—**2nd Annual Advances in Emergency Medicine Seminar: Toxicology and Infectious Disease.** UCLA at San Diego Hilton Beach and Tennis Resort. Fri-Sat. 13.5 hrs. Contact: UCLA.

March 10-12—**Current Concepts on the Pathogenesis and Treatment of Allergic Diseases.** Allergy Foundation of Northern California at Hyatt Lake Tahoe, Nevada. Fri-Sun. 9 hrs. $90. Contact: Professional Communications, (213) 394-3322.

March 10-12—**Controversies in Cholesterol and Aging.** Marin Medical Society and Heart Association at Sonoma Mission Inn & Spa, Sonoma. Fri-Sun. 12 hrs. $325. Contact: Peggy Page, Marin Medical Society, (415) 924-3891.

March 18-19—**26th Annual Clinical Hypnosis Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Sat-Sun. 28 hrs. $350. Contact: Jan Brooks, 615-27th St, San Francisco 94131. (415) 826-0533.

March 18-25—**Primary Care Medicine: Update '89.** UCSF at the Waiohoi, Kauai, Hawaii. 1 week. 20 hrs. $465. Contact: UCSF.

March 19-22—**Annual Meeting of the Society for Adolescent Medicine.** Society for Adolescent Medicine at San Francisco. Sun-Wed. Contact: Edie Moore, 10727 White Oak Ave, Ste 101, Granada Hills 91344. (818) 368-5996.

March 27-29—**Basic Science for Clinicians.** STAN at Stanford Medical Center. Mon-Wed. 16 hrs. $405. Contact: STAN.

March 29-31—**Annual Review in Family Medicine: Pharmacotherapeutics in Primary Care.** USC at Stanford Court Hotel, San Francisco. Wed-Fri. 14 hrs. Contact: Department of Family and Community Medicine, 400 Parnassus Ave, A C9, San Francisco 94143-0900. (415) 476-5250.

April 1-2—**New Drugs and New Indications.** UCSF at Cole Hall. Sat-Sun. 15 hrs. $230. Contact: UCSF.

April 7—**Nora Eccles Harrison Diabetes and Nutrition Update.** UCD at Hyatt Regency, San Francisco. Fri. 5 hrs. $45. Contact: UCD.

April 8—**Antibiotics: 1989 and Beyond.** Grossmont District Hospital at Kona Kai and Tennis Resort, San Diego. Sat. 8 hrs. Contact: Verda Belyeu, CME Office, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

April 12—**Preventive Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

April 12-14—**39th Annual Course for Physicians in Family Practice: Family Practice Update 1989.** Mount Zion Hospital and Medical Center at San Francisco. Wed-Fri. $325. Contact: Family Practice Course, Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

April 13-15—**Recent Advances in Hemophilia Care.** The Hemophilia Treatment Center Orthopaedic Hospital at Los Angeles Hilton. Thurs-Sat. $200. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 14-16—**Office Orthopaedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 29-30—**The Cutting Edge 1989 Erotic Mysteries: Resolving Obstacles to Intimacy.** UCSD at San Diego Marriott Hotel & Marina. Sat-Sun. 12.5 hrs. $295. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 30-May 3—**12th Annual National Conference on Rural Health: Redesigning Rural Health: Blueprints for Success.** National Rural Health Association at Bally's Hotel, Reno, Nevada. Sun-Wed. Contact: Robert Quick, Communications Director. (816) 756-3140.

May 3-5—**10th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Stanford Court, San Francisco. Wed-Fri. $365. Contact: UCSF.

May 10—**Laboratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

May 25-26—**5th Annual Current Issues in Anatomic Pathology.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

June 4-9—**The Power of the Art: Humanism, Healing and Health Care.** Kauai Foundation for Continuing Education and The Hawaii Medical Association at Poipu Beach, Kauai. Sun-Fri. 25 hrs. $395. Contact: David J. Elpern, MD, 3420-B, Kuhio Highway, Lihue, HI 97666. (808) 245-5653.

(Continued on Page 242)

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K-DUR™ 20 | Microburst Release System™
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A daily prophylactic dose in a single tablet.

Please see next page for brief summary of prescribing information.

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K-DUR™ Microburst Release System™
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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE).** There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS);** other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 241)

June 11-16—**Family Practice Refresher Course.** UCI at Newport Beach Sheraton. Sun-Fri. Contact: UCI.

June 23—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 14—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 11-12—**Office Practice Enhancement: Non-invasive Diagnostic Testing.** Medical Education Collaborative at Lake Tahoe, Nevada. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

IDAHO

March 23-24—**Infectious Diseases of the Lung—Idaho Thoracic Society Annual Meeting.** Anderson Center, Boise. Thurs-Fri. Fee: $20, ITS members; $40, nonmembers. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

March 1-4—**New Mexico Metabolism Symposium.** Quail Ridge Inn, Taos. Contact: Kathy Sikes, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

March 2-4—**Santa Fe Ski Symposium—The Kidney in Systemic Disease.** Hotel Eldorado, Santa Fe. Contact: Pat Scott, National Kidney Foundation of NM, 1715 Girard NE, Albuquerque 87106. (505) 266-4573.

March 4—**Common Gastrointestinal Problems of Children.** UNM Nursing/Pharmacy Building, Room 135, Albuquerque. Contact: New Mexico Pediatric Society, UNM School of Medicine, Dept of Pediatrics, Albuquerque 87131. (505) 277-3967.

March 9-11—**Orthopaedic Surgery Conference.** Tammaron at Purgatory. Contact: Kathy Sikes, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

March 31—**James Wiggins Lectureship—Human Papilloma Virus: Its Impact on Women's Care.** Marriott Hotel, Albuquerque. Contact: Office of CME, Presbyterian Hospital, (505) 841-1225.

May 11-13—**New Mexico Medical Society Annual Meeting—A Celebration of the University of New Mexico School of Medicine's 25th Year.** Holiday Inn Journal Center, Albuquerque. Contact: New Mexico Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accred-

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ited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 12-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. The Yarrow, Park City. Contact: (801) 581-8664.

February 20-24—**Fifth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. Park City. Contact: (801) 379-7178.

February 22-25—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott. Contact: (801) 521-1311.

February 22-25—**Rigid Fixation and Craniofacial Anomalies** (Sponsor: UUMC). Wed-Sat. Snowbird. Contact: (801) 581-8664.

February 22-25—**Health/Life Planning: Caring for the Difficult Patient** (Sponsor: UUMC). Wed-Sat. Scottsdale. Contact: (801) 521-2645.

February 25-March 1—**30th Annual OB/GYN Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 521-5501.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

February 26-March 3—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: (801) 581-7553.

March 1-4—**Update in Maternal Fetal Medicine** (Sponsor: UUMC). Wed-Sat. Contact: (801) 581-5501.

March 6-10—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

March 8-11—**Health/Life Planning: Caring for the Difficult Patient** (Sponsor: UUMC). Wed-Sat. St George. Contact: (801) 521-2645.

March 17—**Update in Infectious Diseases** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, Salt Lake City. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 17-18—**Primary Care Orthopedics.** Seattle. Fri-Sat. Contact: U/W.

February 27-March 1—**Current Issues in Infectious Disease.** Seattle. Mon-Wed. Contact: (206) 326-7349.

March 3—**Neurologic Complications of Systemic Disease.** Seattle. Fri. Contact: VMMC.

March 9-10—**Tacoma Academy of Internal Medicine.** Tacoma. Thurs-Fri. Contact: (206) 627-7137.

March 10—**Management of Problem Wounds.** Seattle. Fri. Contact: VMMC.

March 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: U/W, (206) 543-1069.

March 13-23—**PM&R Review.** Seattle. Mon-Thurs. Contact: U/W.

March 20-24—**Drug Therapy.** Maui. Mon-Fri. Contact: U/W.

March 22-23—**Orthopedics and Sports Medicine.** Tacoma. Wed-Thurs. Contact: (206) 627-7137.

March 22-24—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

April 14-15—**Tacoma Surgical Club.** Fri-Sat. Tacoma. Contact: (206) 627-7137.

April 20-21—**Ergonomics.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

April 26-27—**Computers in Medicine (Clinical Applications).** Tacoma. Wed-Thurs. Contact: (206) 627-7137.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069.

May 17—**Neurology.** Tacoma. Wed. Contact: (206) 627-7137.

May 18-19—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

June 1-3—**International Symposium on Pediatric NeuroOncology.** Seattle. Thurs-Sat. Contact: U/W.

June 2—**Current Otology.** Seattle. Fri. Contact: VMMC.

June 26-27—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: (206) 627-7137.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

THE WESTERN JOURNAL OF MEDICINE

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

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Drug names. If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

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Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus*.

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

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This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

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Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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PHYSICIANS WANTED

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall 1988. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

URGENT — FAMILY PRACTICE / GENERAL PRACTICE Physicians needed for excellent solo and group opportunities across the U.S. For information, call (602) 990-8080; or send CV in confidence to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

NORTH IDAHO. Family Physician needed to join four physician group. College and two state universities within the locality. Area provides abundant outdoor recreational opportunities. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294, or 1 (800) 234-1231.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

PHYSICIANS WANTED

JOB OPENING—A rural hospital in southern Utah is seeking the services of an Internal Medicine Specialist to establish practice in the immediate area. This person would be expected to diagnose and treat disease and injury of human internal organ systems, and examine patients for symptoms of organic or congenital disorders and determine nature and extent of injury or disorder using diagnostic aids. This person would also serve as the Medical Director of the hospital's Intensive Care/ Coronary Care Unit. Minimum requirements are a medical degree and completion of an Internal Medicine residency. Hospital will provide office space at no charge for the period of one year. Salary will be $60,000 per year. The position is open immediately and would normally be 40 hours per week, although some call will be expected, particularly in the Intensive Care Unit, and the physician may be asked to work in hospital's emergency room. For further information please contact Utah Job Service, Cedar City Office, 160 E. 200 N., Cedar City, UT 84720; (801) 586-6585, J.O.#0592604.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

INTERNIST. The Visalia Medical Clinic has an opening for a BC/BE General Internist. The Clinic is a 43 physician multispecialty group located in the San Joaquin Valley and central California. Medicine Department consists of five General Internists, along with subspecialties in Cardiology, Endocrinology, Gastroenterology, Medical Oncology and Hematology, Pulmonary Medicine, and also Neurology. Visalia is a progressive city of 65,000 people, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, or Robert A. Havard, Jr, MD, Dept of Internal Medicine, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

PHYSICIANS WANTED

DAR & Associates

Executive Physician Search

FAMILY PRACTITIONERS
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PEDIATRICIAN
OPHTHALMOLOGIST
OB/GYNS
GENERAL SURGEON
ALL SPECIALTIES

Unlike other search firms, **DAR & Associates'** physician recruiters specialize in physician placements exclusively.

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of Beverly Hills
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CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural lifestyles. Contact Dr Donn Cobb, Health Officer, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee-for-service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

ORTHOPEDIST. One day per week. Medical-legal evaluations for traumatic injury patients. No surgery. California license required. Lucrative fee-for-service with high growth potential and guaranteed base. Contact Director, PO Box 14046, San Francisco, CA 94114.

NEW MEXICO. Physicians to share management of general and orthopaedic surgical patients with BC specialists in U.S. Government hospital serving native Americans. Competitive salary and generous fringe benefits. Opportunity to learn, broaden professional capabilities, and enjoy Southwest. Contact E. K. Mehne, MD, Gallup Indian Medical Center, Gallup, NM 87301; (505) 722-1210.

WASHINGTON. General Internist BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is composed of 32 physician multispecialty group. Guaranteed income, plus excellent benefits. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

(Continued on Page 248)

FOR THE SECOND STRAIGHT YEAR, CAP/MPT GIVES REFUNDS AND LOWER RATES

Being a member of CAP/MPT pays in many ways.

For the second consecutive year, we're giving refunds. This year's comes to $8 million. That's as much as $5,015 for some members.

And rates will be lower in 1989. Mature assessments for all but two specialties will be lower than in

A CREDIT TO OUR MEMBERS

1987 and 1988, and more than 12% less in risk classes 1 through 5.

All this is in addition to CAP/MPT's exceptionally low rates each year. Depending on specialty, our members save up to 60% over comparable professional liability protection. There's even an additional reduction for members with a good claims record.

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COOPERATIVE OF AMERICAN PHYSICIANS, INC.

MUTUAL PROTECTION TRUST

Headquarters: Los Angeles

Offices: Orange, San Diego, San Francisco Bay area

The Mutual Protection Trust (MPT) is an unincorporated interindemnity arrangement among physicians authorized by Section 1280.7 of the California Insurance Code. Members do not pay insurance premiums. Instead, they are assessed based on risk classification and number of months of coverage only for the amounts necessary to pay known claims and administrative costs. Members also make an initial trust deposit, which is refundable according to the terms of the trust agreement.

(Continued from Page 246)

PHYSICIANS WANTED

MEDICAL DIRECTOR SOUTHERN CALIFORNIA

Rapidly expanding 10-physician multispecialty group in new 15,000 square foot medical office seeks experienced medical director with BC in primary care or surgical specialty, strong HMO, UR, and committee background. Clinical 75%, administrative 25%. Strong administrative support, well financed, FFS and HMO. Competitive salary, stipend, benefits, profit sharing, and early equity. Call or forward CV to:

Dr Gary L. Groves, Pres.
Pacific Physician Services
Medical Group Network
12 N. Fifth St
Redlands, CA 92373
(714) 825-4401

EUGENE, OREGON. Family Physicians, BE/BC, sought to join growing 36 physician Family Practice/Internal Medicine group in Eugene and nearby rural Cottage Grove. OB optional. Excellent OB support available. Initial income guarantee with incentive. Partnership anticipated after two years. Outstanding schools. Abundant cultural and recreational opportunities. Please send CV or call Rob Daugherty, MD, Oregon Medical Group, 78-A Centennial Loop, Eugene, OR 97401; (503) 688-9140.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

WOFFORD HEIGHTS (FAMILY PRACTICE). Fantastic opportunity for the right physician! New 7,000 square foot multispecialty clinic opening in January 1989. Located in the beautiful mountain lakeside resort community of Wofford Heights, California, an hour east of Bakersfield, this facility will have office and exam space for four physicians. Included will be a pharmacy, full lab, x-ray services. Excellent salary and benefit package. No investment by the physician. Malpractice paid in full. This is a rare opportunity to combine a very attractive lifestyle and an excellent practice opportunity. We are seeking to contract four physicians now. Call George Johnston, (805) 845-3731 for details or write PO Box 457, Lamont, CA 93241.

PULMONOLOGIST. Pulmonologist wanted as associate in very busy Pulmonary/Critical Care practice in Kern County, California. Practice is 100 percent Pulmonary/Critical Care and includes Pulmonary Consultation, Pulmonary Physiology Laboratory, Pulmonary Rehabilitation, Respiratory Care, state-of-the-art Sleep Lab available. Excellent opportunity for BC/BE Pulmonologist looking for potential partnership. Those interested please send CV and inquiries to Dale T. Herriott, MD, Inc, 2525 Eye St, Ste 2B, Bakersfield, CA 93301.

PHYSICIANS WANTED

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Parkway, San Jose, CA 95119; (408) 972-6180.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; telephone 1 (800) 544-1987.

IDAHO. Opportunity for high quality of life, low cost of living in beautiful Idaho—sunbelt of the Pacific Northwest. Join Family Practice teams at one of six multi-site Community/Migrant Health Centers providing primary care to rural communities. Outstanding four-season recreation, malpractice insurance paid, generous continuing education, competitive salary and benefits, loan repayment potential, and opportunity to provide OB services. Send résumé to Dean Hungerford, Idaho Primary Care Association, PO Box 6756, Boise, ID 83707; or call (208) 345-2335.

SAN JOSE, CALIFORNIA. Pre-paid medical group (HMO) looking for dynamic BE/BC residency trained Family Physician. Extensive fringe benefits, including malpractice coverage. Immediately available opening. Send CV to James Conroy, MD, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119; or call (408) 972-6339.

NAPA VALLEY, CALIFORNIA—KAISER PERMANENTE. Well-trained Family Practitioner needed to join a small clinic and provide high quality, personalized care to our patients. Busy office and hospital practice but regular hours. Contact Ernest Arras, MD, 3284 Jefferson, Napa, CA 94558; or call (707) 252-5819.

INTERNIST BE/BC to join growing practice in Tacoma, Washington. Practice is oriented to women's health issues. Women encouraged to apply. Send CV to PO Box 2122, Gig Harbor, WA 98335; (206) 858-8686 evenings.

NORTHERN CALIFORNIA. Family Practice opportunity with Community Health Center. Modesto location. Salary plus incentive program. Spanish fluency desirable. Contact Michael Sullivan, Executive Director, Merced Family Health Centers, Inc, PO Box 858, Merced, CA 95341; (209) 383-1848.

ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

GENERAL INTERNIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

WESTERN WASHINGTON. Otolaryngologist with ENT-Allergy. Sea-ski-golf-fish-hunt-garden etc. Mild climate, good schools, low crime, good location, smaller community, large drawing area. Excellent hospital. Will work with you to help establish. Well equipped office, good crew. Reply to Number 135, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

Physicians wanted for leading clinic

Prestigious Chicago-based clinic group specializing in the treatment of venous disorders is expanding nationally. Our newest clinics in Los Angeles, San Diego and San Francisco are in need of physicians trained in internal medicine—or who have a broad base of medical experience. We will provide complete training in the latest proprietary techniques of treating venous disorders. We offer a six figure salary and bonus potential, along with malpractice insurance and health benefits. And since there are no weekend hours and a 40-hour work week, you will have plenty of leisure time. You won't have to worry about soliciting for patients or fighting insurance companies.

This is an outstanding opportunity for professional and financial advancement. If you are motivated to build a rewarding practice with the leader in the treatment of venous disorders, send your resume to:

Medical Director
Vein Clinics of America
2340 S. Arlington Heights Road
Arlington Heights, Illinois 60005

GASTROENTEROLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

FAMILY PRACTICE, PHOENIX, ARIZONA. BC/BE, private practice, no OB. In-office lab and x-ray. Growing area, southwestern life-style at its best. Located across from modern, full-service hospital. Call (602) 846-7500 or résumé to Westside Family Practice, 5251 W. Campbell Ave, #105, Phoenix, AZ 85031.

INTERNAL MEDICINE DEPARTMENT CHAIRMAN. Maricopa Medical Center of Phoenix, Arizona, is seeking a chairman for its Department of Internal Medicine. We seek a well-qualified individual with recognized credentials in medical education, patient care, and research. Vigorous leadership abilities are required. Duties will include active supervision of the residency and fellowship training programs. The candidate must be BC in Internal Medicine. Maricopa Medical Center is an Equal Opportunity Employer. Those interested should submit inquiries and CV to J. Kipp Charlton, MD, Chairman, Medicine Chairman Search Committee, Maricopa Medical Center, PO Box 5099, Phoenix, AZ 85010.

(Continued on Page 250)

ANNUAL SESSION HIGHLIGHTS

AMERICAN COLLEGE OF PHYSICIANS

presents the

70th Annual Session April 13-16, 1989 Moscone Center, San Francisco, California

A program committed to science and social responsibility--a major event in internal medicine.

- **Clinical Controversies:** experts discuss various aspects of selected disease entities.
- **State of the Art Lectures:** focus on the molecular basis of cell differentiation and growth.
- **Symposia** on Today's Dilemmas: common problems in clinical practice today.
- **Specialty Updates** in all major areas by expert panels.
- **Special Presentations** on a wide variety of subjects of interest to the practitioner.
- **Lectures and Special Workshops** on the latest computer applications in clinical medicine and office practice.
- **Ticketed Programs** including over 200 Workshops, Minicourses and Meet-the-Professor sessions.
- **Two-Day Pre-Session Courses** on Critical Care, Infectious Diseases, and Clinical Decision Analysis; April 11th and 12th.

Savor San Francisco, too.
No other city combines the captivating charm, beauty and sophistication of the city by the Golden Gate. And all of it is easily accessible: the city's finest restaurants and fashionable shops, Fisherman's Wharf, Ghirardelli Square, the Cannery. The cable cars, the vistas, the history, the people.... Come and enjoy this warm, wonderful city—and you, too, just might leave your heart in San Francisco.

How to register:
ALL ACP MEMBERS: complete the registration materials in the Advance Program you received in December.

NON-MEMBERS: please look for a 12-page insert appearing February 1, 1989 in *Annals of Internal Medicine*, with a complete schedule of events and a registration form, or...call 1-800-523-1546, ext. 1229 [in PA, (215) 243-1200, ext. 1229].

PRE-REGISTRATION DEADLINE: February 27, 1989.

AMERICAN COLLEGE OF PHYSICIANS
4200 Pine Street
Philadelphia, PA 19104

A Time for Renewal

(Continued from Page 248)

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

NEUROLOGIST BC/BE. Needed to join rapidly expanding multispecialty group practice in Reno, Nevada (population 350,000). Fee-for-service and pre-paid health care. EEG, EMG, and general Neurology practice with active clinic and hospital bases. Excellent compensation and benefits package including stock options, paid malpractice, and relocation expenses. Interested individuals should submit a CV in confidence to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645, Attn: Janet R. McGee, Manager, Physician Recruitment.

SAN FRANCISCO BAY AREA. Medium-sized multispecialty group practice is seeking a BC/BE Internist to join nine physician Internal Medicine department. Located in the mid-peninsula area adjacent to a 430-bed community hospital and seven miles from Stanford University Medical Center. Competitive salary, incentive plan, and excellent benefits. Opportunity for early partnership. Reply to Number 139, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PRIMARY CARE INTERNIST OR FAMILY PRACTITIONER—BC/BE to join busy expanding fee-for-service/HMO practice in Thousand Oaks, attractive city of 100,000 in Ventura County. Competitive salary and benefits with eventual optional partnership. CV to Sterling Piepgrass, MD, 1400 W. Hillcrest Dr, Newbury Park, CA 91320; (805) 499-1937. Immediate opening.

OREGON. General Internist (BC/BE) sought for busy practice. 10 member multispecialty group. Beautiful rural community. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 471-6161.

ORTHOPAEDIST
Southern California

Orthopaedic Surgeon (Board certified preferred) needed for lucrative, expanding medical practice in Los Angeles area specializing in Worker's Compensation. California license needed as of starting date.

Primarily office practice. Light elective surgical schedule can be limited to arthroscopies.

Virtually no call, evenings or weekends.

Excellent starting salary with possible partnership in less than one year.

Send letter and CV to:

Department WJO
8306 Wilshire Blvd, #7727
Beverly Hills, CA 90211

PHYSICIANS WANTED

EXCELLENT OPPORTUNITY IN SOUTHERN CALIFORNIA
GENERAL SURGEON
EQUITY IN ONE YEAR

Prestigious Orange County based General Surgeon looking for motivated teamplayer who welcomes the opportunity of joining a rewarding, prosperous private practice with state-of-the-art technology.

Excellent suburban environment to raise a family, located in an area of rolling hills, snow-capped mountain views, and horse riding trails. Adjacent to the hospital, free from urban stress, superior schools, beautiful homes attractively priced, and active community involvement.

The position offers an excellent salary, bonus potential, health benefits, and CME.

This is an outstanding opportunity for a BC/BE General Surgeon who is interested in building a solid career in private medical practice. Please send CV or contact:

DAR & Associates Physician Recruiters
250 N. Robertson Blvd, Ste 405
Beverly Hills, CA 90211
1 (800) 922-7PHY
(213) 277-7331

AMBULATORY CARE PHYSICIAN. Veterans Administration Medical Center, Salt Lake City, Utah. Duties include resident supervision and clinical coverage in Admitting/Emergency Care Unit, participation in teaching, research, and administrative functions. Faculty appointment at University of Utah School of Medicine. Position available immediately. Phone (801) 582-1565, ext 1405, or send CV to Nathan Schafer, MD, AO/ECU (11B), VAMC, 500 Foothill, Salt Lake City, UT 84148.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN, Oncologist, or Infectious Disease Specialist at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

CHIEF OF MEDICAL STAFF, HUMBOLDT STATE UNIVERSITY STUDENT HEALTH CENTER. Working under a non-medical Director, the Chief supervises a full outpatient clinic staffed by three MDs, three NPs, and auxiliary staff for approximately 7,000 students. The position is 30 percent medical administration and 70 percent primary care. It pays $65,000/75,000 per year and is a non-tenured management position. Requires Board certification, MD degree, California license, and three years of progressively responsible experience in the practice of medicine. Prefer two years of medical administrative experience. Women and minorities encouraged to apply. For full announcement write Personnel Office, HSU, Arcata, CA 95521.

PACIFIC NORTHWEST—INTERNIST. There are three busy solo Internists, practicing near our 155-bed hospital in Tacoma, Washington, who are seeking associates. They prefer candidates with interest in Geriatrics. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-2, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

FAMILY PRACTICE—SOUTHERN CALIFORNIA. Position available in two physician practice. Rapidly growing area in Fallbrook, one half hour from San Diego. Ideal, close to hospital. Quiet, beautiful setting, near ocean. Contact Thomas Carter, (619) 723-5438.

FAMILY PRACTICE—CENTRAL IDAHO. BC/BE to join hospital managed practice. Salary guarantee plus incentive. All expenses of the practice are paid by the hospital. Low-key practice with boundless recreational opportunities available. Contact John Hull, Administrator, St Mary's Hospital, Box 137, Cottonwood, ID 83522; (208) 962-3251.

SURGEON. Medium-sized multispecialty group practice in San Francisco bay area is seeking a BC/BE General/Vascular Surgeon. Located in the mid-peninsula area adjacent to a 430-bed community hospital and seven miles from Stanford University Medical Center. Competitive salary, incentive plan, and excellent benefits. Opportunity for early partnership. Reply to Number 140, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OCCUPATIONAL / INDUSTRIAL PHYSICIAN needed now to join staff of busy, successful Industrial Medical Clinic located in the growing Santa Maria Valley. Mild climate on central California coast. Malpractice covered. Income negotiable, to be based on minimum guarantee with profit sharing incentive. Prefer experienced Occupational/Industrial Physician. Will consider Family Practice or Emergency Medicine background. Current clinic hours Monday to Friday 7:30-5:30. Send CV to R. D. Shaw, MD, c/o Industrial Medical Group, 3130 Skyway Dr, Ste 702, Santa Maria, CA 93455; (805) 922-8282.

R2, R3 POSITIONS, INTERNAL MEDICINE, LDS HOSPITAL, SALT LAKE CITY, UTAH

An additional R2 position and R3 position are now open in the Internal Medicine Residency Program at LDS Hospital. LDS Hospital is a 520-bed fully accredited teaching hospital affiliated with the University of Utah Medical Center. This is an excellent opportunity for talented individuals to experience a high quality Internal Medicine program in beautiful Salt Lake City, Utah. Positions available July 1, 1989. Write or contact Shauna Bruun, House Staff Coordinator, LDS Hospital, Eighth Ave and C St, Salt Lake City, UT 84143; (801) 321-1077. Equal Opportunity Employer.

(Continued on Page 252)

SPECIAL ISSUES

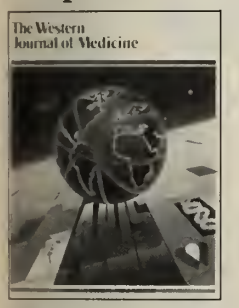
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

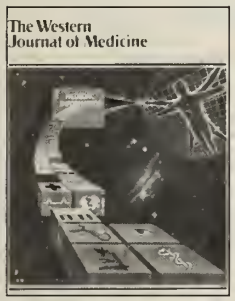
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



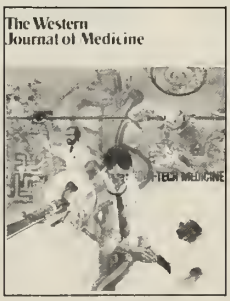
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



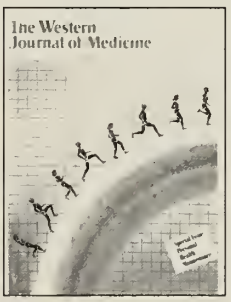
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



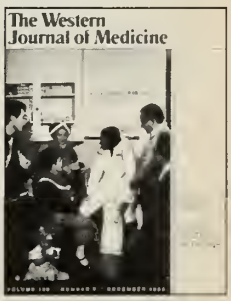
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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11 to 50	3.50
More than 50	3.00

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(Continued from Page 250)

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NORTHERN CALIFORNIA SIERRA FOOTHILLS. Vascular/General Surgeon BC/BE to join established Surgical group. Send CV to Number 137, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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VENTURA (VENTURA COUNTY). Multispecialty group of 42 physicians has an opening for a BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

SOUTHERN CALIFORNIA. Wanted BC Family Practice/Internal Medicine/Emergency Room Physician to join busy two man practice. Liberal salary/benefits. Great opportunity in beautiful recreational community. Call or send CV to Dr Bradley C. Grant, 17037 Lakeshore Dr, Lake Elsinore, CA 92330; (714) 674-6971.

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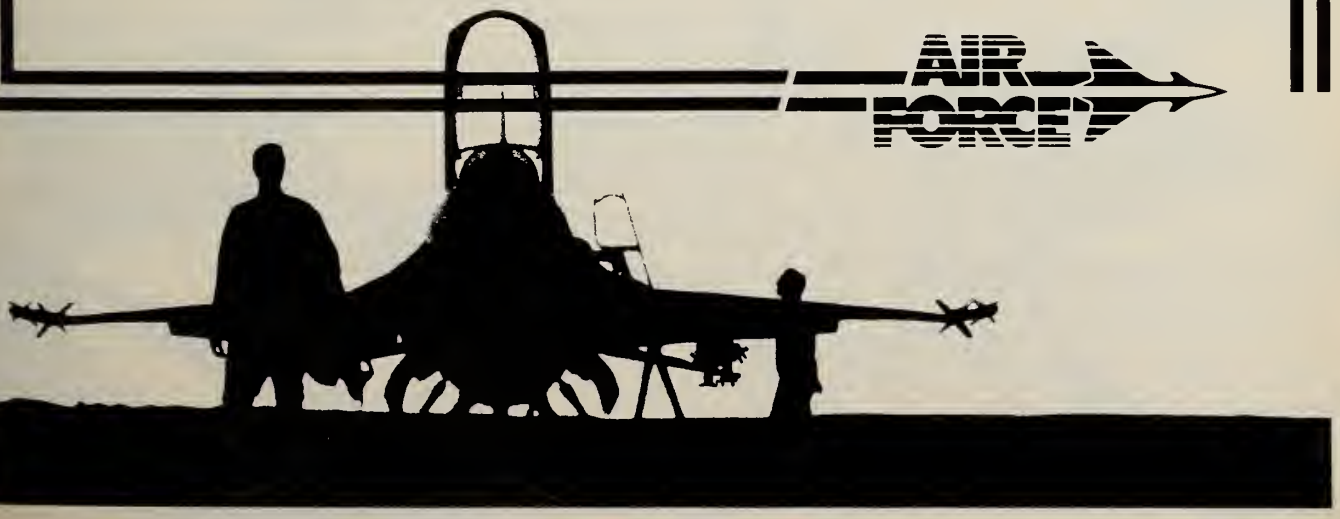

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FAMILY PRACTICE DAY, MARCH 9, 1989, 7:30 A.M.-5:00 P.M. SWEDISH HOSPITAL MEDICAL CENTER GLASER AUDITORIUM. The theme will be Sports Medicine and the goal is to present a medical overview of this special interest, from the problems of competitive athletes to those of the recreational sports enthusiast. For further information contact the Medical Education Office, Swedish Hospital Medical Center, 747 Summit Ave, Seattle, WA 98104; (206) 386-2265.

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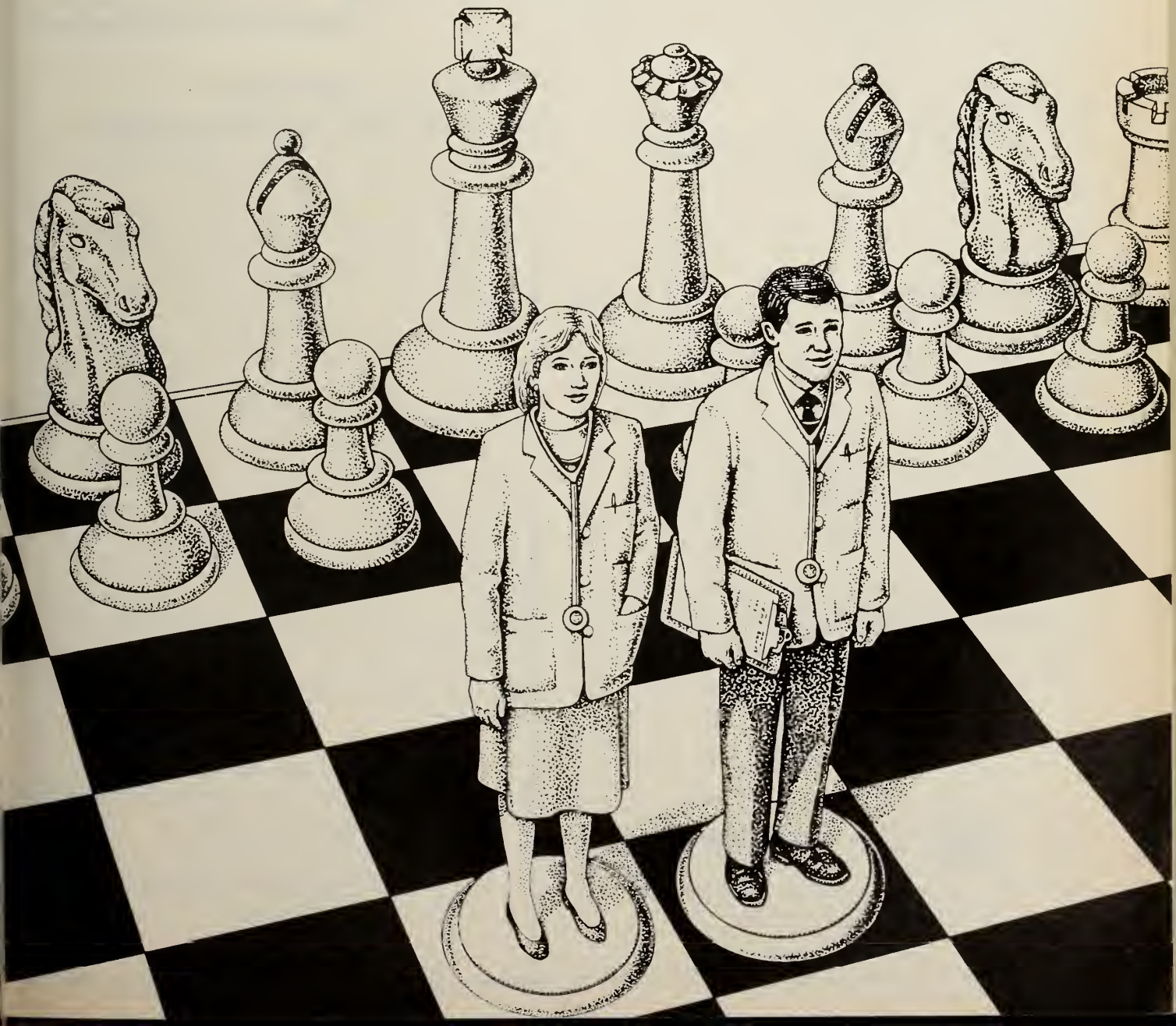

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 1-3, 1989, Pointe at South Mountain, Phoenix.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1989, date and place to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1989, date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1989, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1989, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 1-4, 1989, Ely.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-13, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1989, date and place to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1989, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1989, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1989, date and place to be announced.

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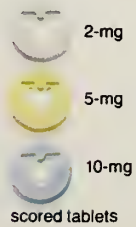

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The portrait of anxiety

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Please see adjacent page for brief summary of prescribing information.

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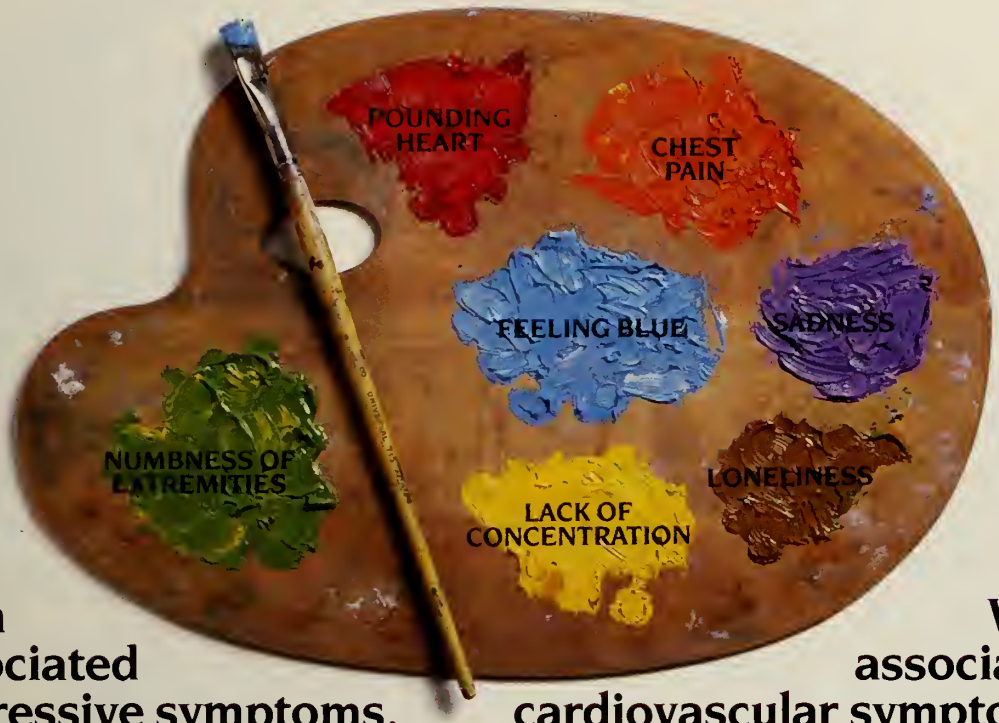
is often complicated



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for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established, periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
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Contraindication: Known allergy to cephalosporins.
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.
Administer cautiously to allergic patients.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever). 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis, elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
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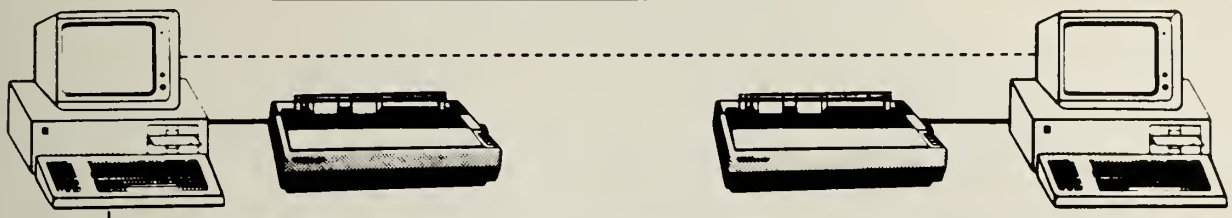

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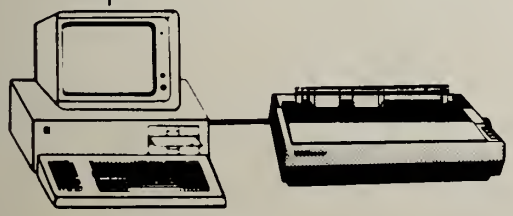

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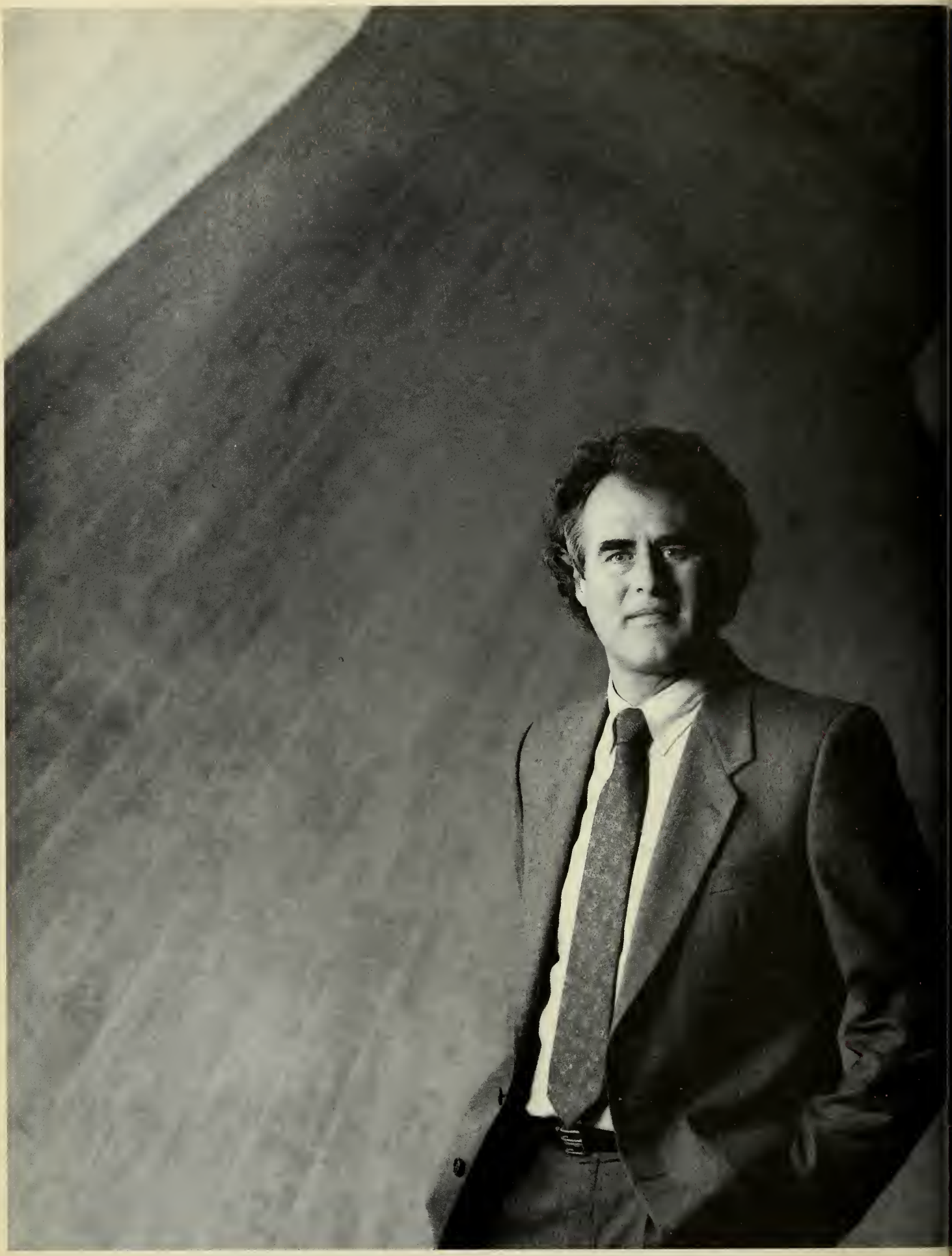

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Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 30-April 1—**25th Annual Arizona Chest Symposium.** Westin LaPaloma, Tucson. Thurs-Sat. Contact: Susan Thornton, Tucson Medical Center, (602) 327-5461, ext 5110.

April 3-4—**Mayo Clinic Scottsdale Clinical Reviews.** The Registry Resort, Scottsdale. Mon-Tues. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

April 28-29—**Recent Advances in Cardiovascular Diseases.** The Registry Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

June 1—**1989 Arizona Medical Association Annual Meeting—Current Perspectives.** The Pointe at South Mountain. Thurs. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 21-22—**Advances in the Diagnosis and Treatment of Allergic Diseases.** UCSF at Hyatt Union Square. San Francisco. Thurs-Fri. $200. Contact: UCSF.

ANESTHESIOLOGY

March 16-19—**Obstetrical Anesthesia: 1989.** UCSF at Hotel Meridien, San Francisco. Thurs-Sun. Contact: Anita Edgecombe, UCSF, C450, Box 0648, San Francisco 94143-0648. (415) 476-2273.

March 18-19—**34th Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

March 16-18—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Westin Maui Hotel. Thurs-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave. KAM314, Los Angeles 90033. (213) 224-7051.

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A Time for Renewal

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

CONTINUING MEDICAL EDUCATION

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March 18-19—**Interventional Cardiology Conference.** UCI at Costa Mesa. Sat-Sun. 12 hrs. Contact: UCI.

March 31-April 1—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 14-15—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Las Vegas, Nevada. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

April 24-May 3—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn. 1½ weeks. 40 hours. $900. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Fisherman's Wharf. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 23-24—**Advanced Cardiac Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

June 24—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

July 15—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: Deborah Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

June 2-3—**Southwestern Regional Cutaneous Flap Workshop.** UCLA Center for Health Sciences. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

June 25—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 16—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

April 5-7—**Advances in Emergency Medicine.** UCSF at Stanford Court, San Francisco. Wed-Fri. $380. Contact: UCSF.

April 26-28—**8th Annual Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Wed-Fri. 17 hrs. Contact: Orange County Trauma Society, 321 N Rampart, Ste 100, Orange 92668. (714) 937-5030.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 19-23—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 23-24—**Advanced Cardiac Life Support.** Center for Health Education at Long Beach. Fri-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 24-25—**11th Annual Poison Center Symposium: Emergency Medicine and Toxicology.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $280. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

January-June—**Seminars in Cytopathology 1989.** UCSF at Health Sciences Room 300. Thurs/monthly. 12 hrs. $140 full series/$30 single. Contact: UCSF.

March 17-18—**Frontiers of Rheumatology.** Annenberg Center for Health Sciences at Eisenhower. Fri-Sun. Contact: ACHS, 39000 Bob Hope Drive, Rancho Mirage 92270.

March 17-19—**Gastroenterology Update Cruise.** Center for Health Education at Queen Mary Hotel, Long Beach. Fri-Sun. 9 hrs. Contact: UCI.

March 17-23—**Internal Medicine 1989: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Fri-Thurs. 54 hrs. $495. Contact: Jacqueline Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 21-24—**Topics in Rheumatology II.** Straub Foundation at Ilikai Hotel, Honolulu, Hawaii. Tues-Fri. 16 hrs. $350. Contact: Juliana J. Woo, MPH, Straub Foundation, 846 S Hotel St, #302, Honolulu, HI 96813. (808) 524-6755.

April 6-7—**Diseases of the Urinary Tract.** Stanford Division of Urology at Hyatt Rickeys Hotel, Palo Alto. Thurs-Fri. 15 hrs. $300. Contact: STAN.

April 8—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. $120. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 14-15—**National Melanoma Conference.** Northern California Cancer Center and Melanoma Foundation at Sir Francis Drake Hotel, San Francisco. Fri-Sat. 9.25 hrs. $225. Contact: Chris Wagner, (415) 595-2704.

April 25-28—**Structural and Chemical Basis for Cell Function.** Annenberg Center for Health Sciences at Eisenhower. Tues-Fri. Contact: ACHS, 39000 Bob Hope Drive, Rancho Mirage 92270.

May 6-7—**Gastroenterology Update.** UCI. Sat-Sun. Contact: UCI.

May 6-13—**Internal Medicine.** STAN at Mauna Kea Beach Hotel, Hawaii. Sun-Fri. 25 hrs. $540. Contact: STAN.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 14-16—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt Union Square. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

September 4-5—**International Conference on Thyroid Metabolism.** UCI at Queen Mary Hotel, Long Beach. Mon-Tues. Contact: UCI.

OB/GYN

March 15-18—**Horizons in Reproductive Health.** UCSD and Planned Parenthood/San Diego at Hotel del Coronado, San Diego. Wed-Sat. 15 hrs. $350. Contact: Carolyn Ferrer, Conference Coordinator, (619) 231-6760.

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CONTINUING MEDICAL EDUCATION

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April 1-2—**Introduction of Vaginal Sonography.** UCI at Hyatt Alicante Hotel, Garden Grove. Sat-Sun. Contact: UCI.

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

June 30-July 4—**7th Annual Controversies in OB/GYN.** UCI at Mauna Kea, Hawaii. Fri-Tues. Contact: UCI.

July 10-12—**Breastfeeding: A Natural World Resource.** La Leche League International at The Anaheim Hilton and Towers. Mon-Wed. 16 hrs. Contact: c/o La Leche League International, 9616 Minneapolis Ave, Franklin Park, IL 60131. (312) 455-7730.

July 29-August 8—**Update in Urogynecology.** UCI at Hawaii. 1 week/2 days. Contact: UCI.

OPHTHALMOLOGY

April 1—**Visions in Ophthalmology '89.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Sat. 5 hrs. $100. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

PEDIATRICS

March 17-18—**Hematology and AIDS: Neonatal & Pediatric Perspectives II.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 12 hrs. $160. Contact: Kim 1. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 30-April 1—**Pediatric Trends.** American Academy of Pediatrics at Waiohai Hotel, Kauai, Hawaii. Thurs-Sat. 16 hrs. Contact: CME Registration, Department of Education, AAP, PO Box 927, Elk Grove Village, IL 60009-5005. (800) 433-9016.

April 1—**Ethical Issues in Pediatrics.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

April 5-7—**14th Annual Symposium on Care of the Sick Newborn.** UCI at Hyatt Regency Hotel, Long Beach. Wed-Fri. Contact: UCI.

April 14-16—**2nd Annual Pediatrics in Progress.** American Academy of Pediatrics at Las Vegas. Fri-Sun. 18 hrs. Contact: American Academy of Pediatrics, Dept of Education, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016 ext 7657.

April 15—**New Information on Old Exanthems.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Immunizations: Current and Future Vaccines.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Menstrual Problems in Adolescents.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Common Presentations of Uncommon Conditions; Uncommon Presentations of Common Conditions.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 27-28—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott. Thurs-Fri. Contact: UCI.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 273)

June 10—**Atherosclerosis; Pathogenesis and Screening.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Hypertension in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Office Evaluation of Sports Injuries.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Fitness Training in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

July 18—**22nd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel Nob Hill, San Francisco. Thurs-Sat. 16 hrs. $275. Contact: UCSF.

RADIOLOGY

April 16-21—**9th Annual San Diego Residents Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 28-30—**14th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

May 2-6—**9th Annual Mid-Pacific Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Royal Waikoloan Hotel, The Big Island of Hawaii. Tues-Sat. 19 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078

July 27-30—**3rd Annual Symposium on Magnetic Resonance Imaging.** Ritz-Carleton Resort Hotel, Laguna Niguel. Thurs-Sun. 23 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 31-August 4—**Modern Radiology Practice.** UCSD at Four Seasons Biltmore Hotel, Santa Barbara. Mon-Fri. 24 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

January-July—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 15-17—**Perioperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. $350. Contact: UCSF.

March 16-19—**Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 6-8—**Postgraduate Course in General Surgery.** UCSF at San Francisco Hilton. Thurs-Sat. Contact: UCSF.

May 6-13—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Hawaii. Sun-Fri. 25 hrs. $450. Contact: STAN.

May 20—**6th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic Surgery Medical Group at La Jolla Marriott Hotel. Mon. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

OF INTEREST TO ALL PHYSICIANS

March 18-19—**26th Annual Clinical Hypnosis Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Sat-Sun. 28 hrs. $350. Contact: Jan Brooks, 615-27th St, San Francisco 94131. (415) 826-0533.

March 18-25—**Primary Care Medicine: Update '89.** UCSF at the Waiohoi, Kauai, Hawaii. 1 week. 20 hrs. $465. Contact: UCSF.

March 19-22—**Annual Meeting of the Society for Adolescent Medicine.** Society for Adolescent Medicine at San Francisco. Sun-Wed. Contact: Edie Moore, 10727 White Oak Ave, Ste 101, Granada Hills 91344. (818) 368-5996.

March 20-21—**HIV: A Multidisciplinary Approach.** Community Hospital of Sonoma County. Red Lion Inn, Rohnert Park. Mon-Tues. 12 hrs. $180. Contact: Community Hospital of Sonoma County, 3325 Chanate Rd, Santa Rosa 95404. (707) 576-4551.

March 27-29—**Basic Science for Clinicians.** STAN at Stanford Medical Center. Mon-Wed. 16 hrs. $405. Contact: STAN.

March 29-31—**Annual Review in Family Medicine: Pharmacotherapeutics in Primary Care.** USC at Stanford Court Hotel, San Francisco. Wed-Fri. 14 hrs. Contact: Department of Family and Community Medicine, 400 Parnassus Ave, A C9, San Francisco 94143-0900. (415) 476-5250.

April 1-2—**New Drugs and New Indications.** UCSF at Cole Hall. Sat-Sun. 15 hrs. $230. Contact: UCSF.

April 7—**Nora Eccles Harrison Diabetes and Nutrition Update.** UCD at Hyatt Regency, San Francisco. Fri. 5 hrs. $45. Contact: UCD.

April 8—**Antibiotics: 1989 and Beyond.** Grossmont District Hospital at Kona Kai and Tennis Resort, San Diego. Sat. 8 hrs. Contact: Verda Belyeu, CME Office, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

April 12—**Preventive Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

April 12-14—**39th Annual Course for Physicians in Family Practice: Family Practice Update 1989.** Mount Zion Hospital and Medical Center at San Francisco. Wed-Fri. $325. Contact: Family Practice Course, Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

April 13-15—**Recent Advances in Hemophilia Care.** The Hemophilia Treatment Center Orthopaedic Hospital at Los Angeles Hilton. Thurs-Sat. $200. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 14-16—**Office Orthopaedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 19-21—**8th Annual Bright Horizons in Respiratory Care.** Annenberg Center for Health Sciences at Eisenhower. Wed-Fri. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270.

April 19-22—**4th International Symposium: Gyn/Onc/Surg/Urol.** UCI at Newport Beach Sheraton. Wed-Sat. 15 hrs. Contact: UCI.

April 29-30—**Clinical Strategies for the Primary Care Physician: Focus on the Aging Patient.** American Academy of Family Physicians Santa Clara at Monterey Conference Center Steinbeck Forum. Sat-Sun. 9 hrs. $150. Contact: Eugene Greider, MD, 877 Fremont Ave, Bldg J, Sunnyvale 94087. (408) 736-2304.

April 29-30—**The Cutting Edge 1989 Erotic Mysteries: Resolving Obstacles to Intimacy.** UCSD at San Diego Marriott Hotel & Marina. Sat-Sun. 12.5 hrs. $295. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 30-May 3—**12th Annual National Conference on Rural Health: Redesigning Rural Health: Blueprints for Success.** National Rural Health Association at Bally's Hotel, Reno, Nevada. Sun-Wed. Contact: Robert Quick, Communications Director. (816) 756-3140.

May 3-5—**10th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Stanford Court, San Francisco. Wed-Fri. $365. Contact: UCSF.

May 10—**Laboratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

May 25-26—**5th Annual Current Issues in Anatomic Pathology.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

(Continued on Page 286)

STOP LESIONS FROM SURFACING

An alarming rise in the incidence of genital herpes points to the need for better disease treatment. Fortunately, long-term maintenance therapy with ZOVIRAX® can help keep herpes patients lesion-free. In controlled studies of 4 to 6 months' duration, recurrences were totally prevented in up to 75% of patients. And during two years of clinical use, daily therapy has been shown to be generally well tolerated.[1] One capsule TID...the best way to stop lesions from surfacing.

Reference. 1. Data on file, Burroughs Wellcome Co.

ZOVIRAX®
(acyclovir) **capsules**

Keeps herpes patients lesion-free longer

Please see brief summary of prescribing information on next page.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

Burroughs Wellcome Co.,
Research Triangle Park,
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ZOVIRAX®
(acyclovir) capsules

Daily therapy helps keep patients lesion-free longer*

Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories.

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤10 ml/min/1.73 m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).

Store at 15°-30°C (59°-86°F) and protect from light and moisture.

U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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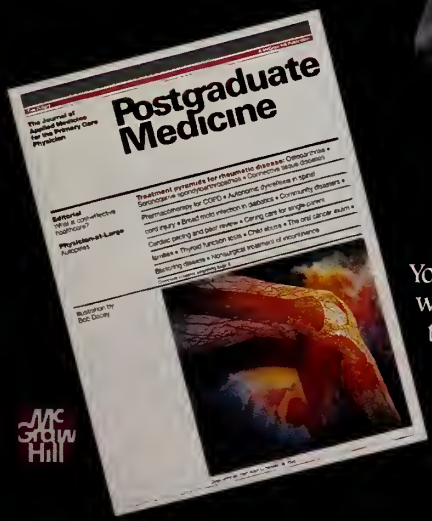

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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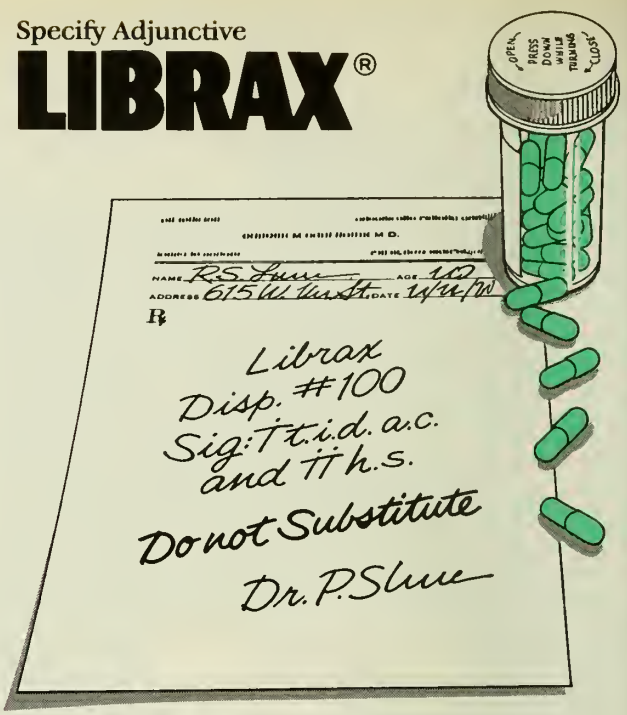

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

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Please see summary of prescribing information on adjacent page.

In Memoriam

Arizona Medical Association

ALEXANDER, MANFRED, Phoenix. Died Dec 5, 1988, aged 61. Graduate of New York Medical College, Valhalla, NY, 1954. Licensed in Arizona in 1975. Dr Alexander was a member of the Maricopa County Medical Society.

ANDERSEN, JOHN T., Tucson. Died Nov 3, 1988, aged 53. Graduate of University of Minnesota Medical School, Minneapolis, 1961. Licensed in Arizona in 1986. Dr Andersen was a member of the Pima County Medical Society.

CUTCHER, SOLOMON, Tucson. Died Nov 3, 1988, aged 71. Graduate of University of Mississippi School of Medicine, Jackson, 1962. Licensed in Arizona in 1963. Dr Cutcher was a member of the Pima County Medical Society.

HAWKINS, LYNN K., Scottsdale. Died Sep 13, 1988, aged 59. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1955. Licensed in Arizona in 1962.

SHUPE, REED D., Phoenix. Died Dec 13, 1988, aged 85. Graduate of George Washington University School of Medicine, Washington, DC, 1933. Licensed in Arizona in 1962. Dr Shupe was a member of the Maricopa County Medical Society.

STEVES, RICHARD J., Sun City. Died Sep 13, 1988, aged 77. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in Arizona in 1983.

SUTTON, JAMES A., Tucson. Died Dec 10, 1988, aged 74. Graduate of Temple University School of Medicine, Philadelphia, 1939. Licensed in Arizona in 1949. Dr Sutton was a member of the Pima County Medical Society.

YOUNT, FLORENCE B., Prescott. Died Nov 25, 1988, aged 79. Graduate of George Washington University School of Medicine, Washington, DC, 1934. Licensed in Arizona in 1936. Dr Yount was a member of the Yavapai County Medical Society.

California Medical Association

BEBENSEE, DONALD L., Santa Clara. Died Oct 19, 1988, aged 57. Graduate of University of Western Ontario, 1955. Licensed in California in 1963. Dr Bebensee was a member of the Santa Clara County Medical Society.

EDGAR, ERWOOD G., Orange. Died Oct 23, 1988, aged 72. Graduate of Harvard Medical School, Boston, 1941. Licensed in California in 1945. Dr Edgar was a member of the Orange County Medical Association.

FALICOV, RAUL ESTEBAN, La Mesa. Died Sep 14, 1988, aged 51. Graduate of University of Buenos Aires, 1960. Licensed in California in 1977. Dr Falicov was a member of the San Diego County Medical Society.

GAMPELL, RAPHAEL J., Los Altos. Died Oct 3, 1988, aged 71. Graduate of University of Manchester, England, 1940. Licensed in California in 1950. Dr Gampell was a member of the Santa Clara County Medical Society.

GAVIN, MARTIN J., Jr, Anaheim. Died Oct 27, 1988, aged 71. Graduate of University of Southern California, 1953. Licensed in California in 1953. Dr Gavin was a member of the Orange County Medical Association.

KAPLUS, ALBERT, Villa Park. Died Sep 15, 1988, aged 65. Graduate of Chicago College of Osteopathic Medicine, 1950. Licensed in California in 1976. Dr Kaplus was a member of the Orange County Medical Association.

NAKAZATO, HIROHARU H., Pinole. Died Sep 22, 1988, aged 59. Graduate of University of Nagoya, Japan, 1954. Licensed in California in 1960. Dr Nakazato was a member of the Alameda-Contra Costa Medical Association.

PEREYRA, ARMAND J., Ontario. Died Oct 14, 1988, aged 84. Graduate of University of California Medical School, 1930. Licensed in California in 1930. Dr Pereyra was a member of the San Bernardino County Medical Society.

POOL, GEORGE F., Pleasanton. Died Aug 13, 1988, aged 79. Graduate of Loma Linda University, 1948. Licensed in California in 1948. Dr Pool was a member of the Alameda-Conta Costa Medical Association.

SHER, RALPH M., Huntington Beach. Died Oct 20, 1988, aged 64. Graduate of University of California, San Francisco, 1951. Licensed in California in 1951. Dr Sher was a member of the Orange County Medical Association.

SNYDER, J. FREDERIC, San Jose. Died Oct 9, 1988, aged 73. Graduate of Temple University School of Medicine, Philadelphia, 1941. Licensed in California in 1946. Dr Snyder was a member of the Santa Clara County Medical Society.

WEAVER, JOHN C. Died Dec 16, 1988, aged 76. Graduate of University of Virginia, 1940. Licensed in California in 1947. Dr Weaver was a member of the Alameda-Contra Costa Medical Association.

New Mexico Medical Society

LYLE, EDWARD H., Albuquerque. Died Nov 1988, aged 83. Graduate of Baylor College of Medicine, Houston, 1929. Licensed in New Mexico in 1946. Dr Lyle was a member of the Greater Albuquerque Medical Association.

MILLER, ROBERT J., Los Alamos. Died Dec 1988, aged 65. Graduate of University of Oklahoma Medical School, 1947. Dr Miller was a member of the Los Alamos County Medical Society.

Utah Medical Association

MCALLISTER, ARTHUR JAMES, Salt Lake City. Died Aug 21, 1988, aged 68. Graduate of University of Utah, 1944. Licensed in Utah in 1946. Dr McAllister was a member of the Salt Lake Medical Society.

MAYBERRY, PAUL R., Moab. Died Sep 17, 1988, aged 66. Graduate of George Washington University, Washington, DC, 1952. Dr Mayberry was a member of the Southeastern Utah Medical Society.

CARAFATE®
(sucralfate) Tablets

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE
There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:
1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987; 9(4):395-399

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Please see brief summary of prescribing information, and reference on adjacent page.

0160N8

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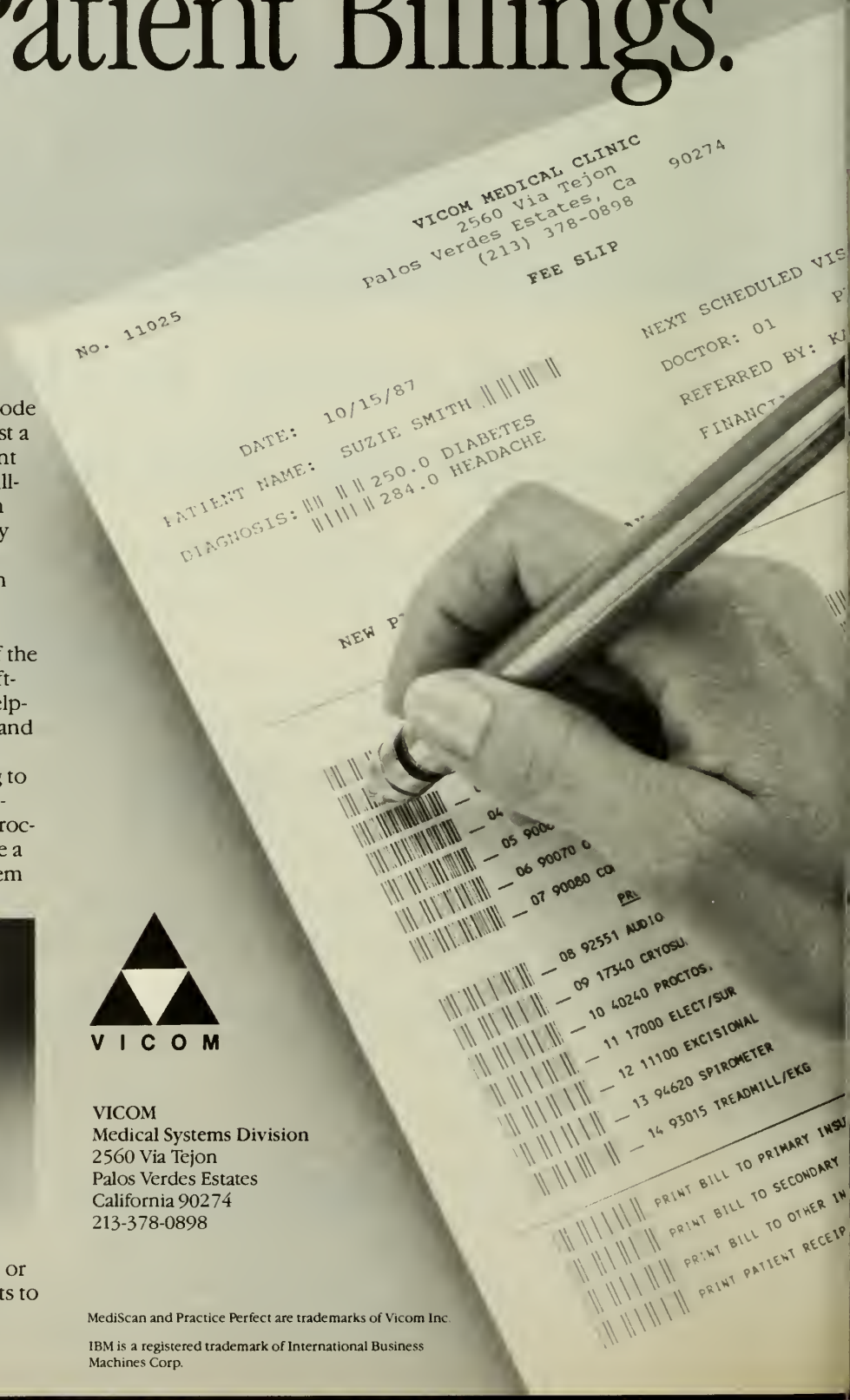

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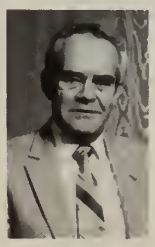
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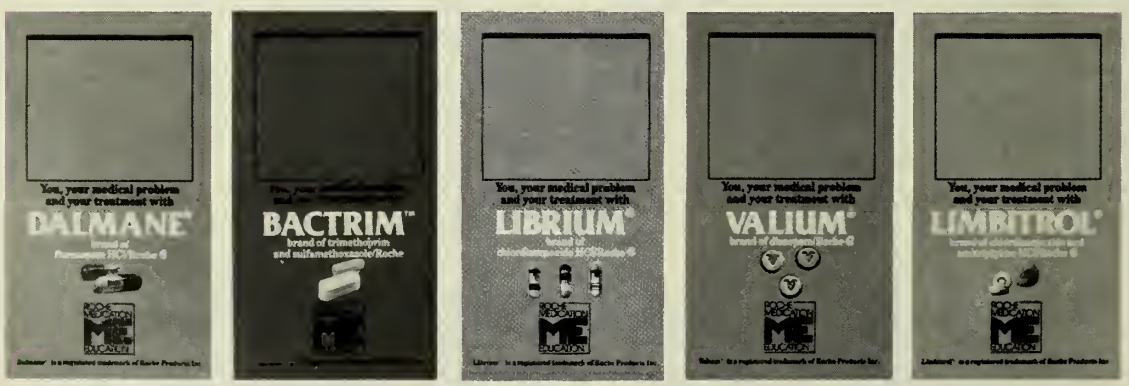

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Transdermal Infusion System

Easy to open... apply... remove.

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Please see next page for brief summary of prescribing information. Copyright © 1988, Key Pharmaceuticals, Inc., Kenilworth, NJ 07033. All rights reserved.

Nitro-Dur®
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Transdermal Infusion System

- **Easy opening**—even for arthritic hands.
- **Round-the-clock cling**—lies flat, holds tight.
- **Hard to notice, easy to wear**—semitransparent, soft and flexible.
- **Push-button removal**—just a press in the center raises the rim for easy lift-off.

BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. EDP #I030160
Revised 09/87 14362304

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All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA

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ND-2142/14579303

CONTINUING MEDICAL EDUCATION

(Continued from Page 274)

June 4-9—**The Power of the Art: Humanism, Healing and Health Care.** Kauai Foundation for Continuing Education and The Hawaii Medical Association at Poipu Beach, Kauai. Sun-Fri. 25 hrs. $395. Contact: David J. Elpern, MD, 3420-B, Kuhio Highway, Lihue, HI 97666. (808) 245-5653.

June 11-16—**Family Practice Refresher Course.** UCI at Newport Beach Sheraton. Sun-Fri. 30 hrs. Contact: UCI.

June 23—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 9-12—**3rd Annual Family Practice Board Review.** UCSD at Hanalei Hotel, San Diego. Sun-Wed. 20 hrs. $355. Contact: Janice R. Turner, PO Box 2528, La Jolla 92038. (619) 459-9597.

July 10-13—**Family Practice Board Review Course.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Thurs. 25 hrs. Contact: Division of Family and Community Medicine, 400 Parnassus Ave, A-C9, San Francisco 94143-0900. (415) 476-1482.

July 14—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 11-12—**Office Practice Enhancement: Non-invasive Diagnostic Testing.** Medical Education Collaborative at Lake Tahoe, Nevada. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 8-9—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Napa. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 13-15—**Primary Care Medicine: Principles and Practice.** UCSF at The Portman, San Francisco. Wed-Fri. 20 hrs. $385. Contact: UCSF.

IDAHO

March 23-24—**Infectious Diseases of the Lung—Idaho Thoracic Society Annual Meeting.** Anderson Center, Boise. Thurs-Fri. Fee: $20, ITS members; $40, nonmembers. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

May 7-10—**Idaho Academy of Family Physicians—Annual Meeting.** Coeur d'Alene Convention Center. Sun-Wed. Contact: Irma Sparks, Exec Dir, Idaho Academy of Family Physicians, PO Box 175, Boise 83701. (208) 362-4808.

July 27-29—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 31—**James Wiggins Lectureship—Human Papilloma Virus: Its Impact on Women's Care.** Marriott Hotel, Albuquerque. Contact: Office of CME, Presbyterian Hospital, (505) 841-1225.

May 11-13—**New Mexico Medical Society Annual Meeting—A Celebration of the University of New Mexico School of Medicine's 25th Year.** Holiday Inn Journal Center, Albuquerque. Contact: New Mexico Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

(Continued on Page 288)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 286)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

March 17—**Update in Infectious Diseases** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, Salt Lake City. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

(Continued on Page 291)

ARMY RESERVE MEDICAL PROFILE NO. 5

ROSALYN P. STERLING-SCOTT, M.D.

Assistant Professor of Surgery, UCLA School of Medicine and Drew University of Medicine and Science, Los Angeles

Associate Surgeon, Department of Cardiovascular & Thoracic Surgery, Centinela Hospital Medical Center, Los Angeles

Major, U.S. Army Reserve

EDUCATION Rensselaer Polytechnic Institute, Troy, NY, B.S. Chemistry; NYU School of Medicine, New York, M.D.

RESIDENCY Boston University School of Medicine (Cardiovascular); Saint Vincent's and St. Claire's Hospitals, New York City (General Surgery)

FELLOWSHIP First Mary A. Fraley Cardiovascular Surgical Research Fellow at the Texas Heart Institute, Houston

OUTSTANDING ACHIEVEMENTS Author of numerous articles, including "Indications for Early Bypass Grafting Following Intracoronary Streptokinase"; author of "The Female Surgeon—Dawn of a New Era," chapter in *A Century of Black Surgeons—The U.S.A. Experience*; Board of Directors, Association of Black Cardiologists; Secretary, Drew Society

"The caliber of physicians you meet in the Army Reserve exposes you to new ways of looking at a problem. It's easy for young surgeons to become entrenched in one method, but in the Army Reserve you'll have the chance to work with outstanding physicians in your own specialty, and often learn new ideas that will help you to improve your own approach to clinical or research problems," says Dr. Sterling-Scott.

The Army Reserve can offer physicians a variety of challenging options such as teaching, research, unique training programs, and the opportunity to practice in prestigious Army medical centers.

"Joining the Army Reserve enabled me to take advantage of a number of conferences, including one at Walter Reed, where I worked with thoracic surgical colleagues, while conducting my own research project."

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For respiratory tract infections due to susceptible strains of indicated organisms.

Summary.
Consult the package literature for prescribing information.

Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS
Administer cautiously to allergic patients
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include
- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme (rarely, Stevens-Johnson syndrome) and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever): 1.5%, usually subside within a few days after cessation of therapy Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly) [061088L]

Additional information available from PV 2351 AMP
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CONTINUING MEDICAL EDUCATION

(Continued from Page 288)

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 20-24—**Drug Therapy.** Maui. Mon-Fri. Contact: U/W.

March 22-23—**Orthopedics and Sports Medicine.** Tacoma. Wed-Thurs. Contact: (206) 627-7137.

March 22-24—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

April 11, 13—**AIDS Education.** Seattle. Tues, Thurs. Contact: UW, (206) 543-3910.

April 14-15—**Tacoma Surgical Club.** Fri-Sat. Tacoma. Contact: (206) 627-7137.

April 20-21—**Ergonomics.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

April 22—**AIDS Education.** Spokane. Sat. Contact: UW, (206) 543-3910.

April 26-27—**Computers in Medicine (Clinical Applications).** Tacoma. Wed-Thurs. Contact: (206) 627-7137.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069.

May 17—**Neurology.** Tacoma. Wed. Contact: (206) 627-7137.

May 18-19—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

May 20—**AIDS Education.** Everett. Sat. Contact: UW, (206) 543-3910.

June 1-3—**International Symposium on Pediatric NeuroOncology.** Seattle. Thurs-Sat. Contact: U/W.

June 2—**Current Otology.** Seattle. Fri. Contact: VMMC.

June 26-27—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: (206) 627-7137.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 8-10—**Wyoming Medical Society—Annual Meeting.** Teton Lodge, Jackson. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. ◆

DYAZIDE®
25 mg. Hydrochlorothiazide/50 mg. Triamterene/SKF

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

Indications and Usage: *Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.*

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia), anuria, acute and chronic renal insufficiencies or significant renal impairment, hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

Warnings *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.*

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions *The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease, potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days, attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low salt milk (may contain up to 60 mEq of potassium per liter); potassium containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions *The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants, thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

Supplied: *Capsules containing 25 mg. hydrochlorothiazide and 50 mg. triamterene, in bottles of 1000 capsules, in Single Unit Packages (unit dose) of 100 (intended for institutional use only), in Patient-Pak™ unit-of-use bottles of 100.*

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

MARCH 1989, VOL. XLVI, NO.3

Bruce Robinson Remembered

Marshall B. Block, M.D.

It was fifteen years ago when I first met Bruce. Having come here from Colorado, fresh out of an academic environment, I contacted Bruce to see if *Arizona Medicine* could use my services in writing an endocrinology and metabolism column. With the support of John Kennedy, who was then editor of *Arizona Medicine*, the column came to fruition. After about two years, when John was ready to retire as editor, Bruce called me and said, "Anyone who writes as many articles for a magazine as you do, ought to be its editor." Thus, was started my tenure with *Arizona Medicine* and my association with Bruce.

Through the years, Bruce had been most supportive of the journal and understood the importance of its existence for the identity of *Arizona Medicine*. Although it never became another *New England Journal of Medicine*, it did serve as a format for local physicians to contribute to the continuing education of their peers. As such, it allowed those of us who had the talent to write to do so. The changes in style and format which ensued over the last twelve years or so, were based upon need and finances. All major decisions regarding *Arizona Medicine* were carefully considered by Bruce who helped in shaping the future of the journal.

During this period of contact with Bruce, it became apparent to me that he exhibited very special skills in leadership. To deal with the ever changing personalities in ArMA in a constructive manner in order to ensure the continued success of the organization was, indeed, a difficult task. It would have been hard enough if the persons involved were not physicians, but being physicians made the job even more difficult. The strong, opinionated and aggressive nature of most physicians was sometimes difficult to reconcile with the ongoing nature of his job. But, somehow Bruce was capable of harnessing even those energies and putting them to the best use of the organization. I sometimes wondered how he did it. I was privileged to serve as his personal physician several years later and began to understand the storm beneath the calm waters. It was only then that the true cost of managing such a large enterprise, as the Arizona Medical Association, became apparent.

All of us who have been members of ArMA owe a great deal to Bruce Robinson who, during several turbulent periods, kept our ship afloat and guided us in the right direction. He gave more of himself to our Association than most of us will ever understand.

The words of those who knew him in differing capacities through the years, follows in the ensuing pages of this memorial issue to Bruce. A common thread that ties all aspects of his life together is that of a concerned, caring and dedicated individual who placed the interests of the Association above those of any one individual or group.

The Arizona Medical Association has, indeed, lost a true friend. However, Bruce's tragic loss should not be in vain. His ideals and dedication should be remembered. Perhaps they already are as exemplified by the strong and dominant pillars that support our building on Bethany Home Road. It can be envisioned as "the house that Robinson helped build."

Marshall B. Block, M.D., Editor

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

MARCH 1989, VOL. XLVI, NO. 3

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From Our President

Richard L. Collins, M.D.

As I indicated in my column in the February issue of Arizona Medicine, this March issue will be dedicated to Bruce E. Robinson, who had been with ArMA for almost twenty-five years and was Executive Vice President for eighteen. His untimely death at the age of 61 ended that association in December of last year.

Bruce was born in Cordelia, California, and was raised in Oakland, eventually graduating from the University of Washington with a B.A. degree, having majored in management and with minor studies in psychology.

Bruce came to Arizona from Alaska, where he had spent several years as Controller of the Northern Commercial Company, and then as director of operations during the building and opening of a private hospital in Anchorage.

Prior to that he lived in Seattle, where he was associated with the medical field through his work in a psychiatric hospital. It was there that he met his wife-to-be, the former Berry Jane Jones, a psychiatric nurse.

Betty and Bruce had two sons and a daughter, and there are four grandchildren. One of his sons is a physician in Phoenix, having apparently acquired his interest in the medical field through his father.

With this brief introduction, I would like to invite you to read the comments of physicians in Arizona and executive colleagues from throughout the country regarding their memories during years of association with Bruce in his professional life.

We, at ArMA, will miss him. Hopefully, we can change this adversity to opportunity and step forward.

Richard L. Collins, M.D., President

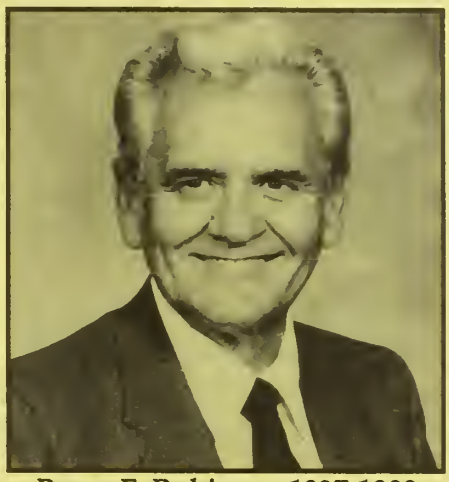
—AMA—

I was fortunate to have known and worked with Bruce over a span of many years; during that time, he was a valuable source of advice and counsel. In his capacity as a long-time member of the Advisory Committee to the AMA Executive Vice President, Bruce always offered thoughtful opinions, well-balanced ideas and an open mind.

Bruce was also recognized by his medical society colleagues for the contributions he made towards the betterment of those within the medical community. He held a number of important positions within the hierarchy of the American Association of Medical Society Executives, including the Presidency of AAMSE during 1986-87. That is the highest honor a medical society executive can receive from his peers.

Bruce was advisor, counsel and friend. We are all more accomplished members of our profession for having crossed paths with him.

James H. Sammons, M.D.
Executive Vice President
American Medical Association



Bruce E. Robinson 1927-1988

—ArMA—

We remember Bruce in many different ways. Except for a spouse or other immediate family who lives with a person over the long haul, who "knows" an individual better than those who work with him, especially if he is "the boss?"

We remember Bruce for the soft-spoken way in which he handled most situations which arose in the office, for his confidence in his decisions, for the obvious fact that his first concern was always what was best for ArMA, for his pride in the Association, and for insisting that ArMA's image to the world outside our walls be of the highest quality. He demanded the best of us, and we were challenged to perform up to his standards.

We remember him also for his kindness and thoughtfulness when one of us had a serious personal problem, and for allowing "time off" for us to try to resolve them.

We were always aware of the fact that ArMA was first and foremost "the doctors' organization," and our first duty was to see that we did everything possible for the members so that they would want to remain members and be proud of their organization. Even when he or we did not agree completely with the positions taken by ArMA, we knew that we were expected to support those positions in any public forums. And Bruce was a leader and example in this effort.

It is difficult to condense in one short article the many memories of the man we worked for, some for many years and some for only a short time. But the shock of his sudden and unexpected death has made us aware that there was much we did not know or understand about him--and leaves us all wondering just how much anyone ever really knows about what is going on inside another person.

We will always remember Bruce, and sincerely hope that he has found peace.

The ArMA Staff

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When I think of my countless contacts with Bruce Robinson, I always go back to an episode in the early 60s. It was 7:00 or 8:00 p.m. and I was still at one of the hospitals. Satisfied with the patient's status, a concern relating to an ArMA problem led to a phone call to Bruce for his opinion. Rather than discuss it by telephone, he suggested we meet somewhere eye to eye. We did, and for over an hour explored the problem in depth from every angle.

My last contact with Bruce was at the ArMA meeting in Tucson last year. Although I then had vastly fewer problems, it was the same Bruce smiling, affable, deeply concerned with medicine in general and ArMA in particular.

This is the Bruce I have known for well over 25 years. No matter how trivial or serious the problem, he was always eager to help a friend in need. A memory to cherish.

Al Brewer, M.D.
ArMA President
1964-65

Bruce was the "core" of the medical society--he held it together as he dealt with the diversity and special interests of rotating officers and committees.

He was a gentle man, who always had an understanding, optimistic word to say about most situations and physicians despite the associated problems. I know I depended heavily on his guidance and reasoned judgment.

Bruce was a credit to medicine, and he made our profession become a functioning part of society as a whole by identifying that we as physicians had social responsibilities beyond caring for people.

Bruce will be missed, and I will always honor his memory.

Bill Crisp, M.D.
ArMA President, 1979-80

As ArMA was noticeably growing in the early years of 1963-64 due to the influx of physicians to our State, Bruce was among those interviewed as Assistant for my then office of Executive Secretary to the Arizona Medical Association. He personally impressed me and I never regretted, in the five years we worked together, that I was able to present him to "my doctors," for their approval. He adapted readily and I found him always proper and loyal. I was deeply saddened to learn of our loss.

Bob Carpenter
ArMA Honorary Past President,
Retired Executive Secretary,
ArMA, 1950-1969

PAST PRESIDENTS

Bruce was always courteous and thoughtful. I had no serious problems with him way back then. I thought he was a good administrator.

Carlos C. Craig, M.D.
ArMA President 1957-58

On Tap, But Not On Top

As I try to help commemorate the passing of Bruce E. Robinson, the plaque presented to me after my presidency keeps catching my eye. It was the first of a kind, having the picture of the recipient embedded in it. It was presented by the incoming president as was customary. But it was conceived by Bruce and handed to the new president by Bruce who was crouched behind the stage, invisible to the audience. As always, he was behind the scenes, keeping us informed, giving class to our organization, and guiding us through the troubled times we faced on behalf of ArMA and Arizona physicians.

Typical was how he helped handle the Health Planning Authority and the State Health Plan. Massive documents were put together with no input from ArMA, given to us just before meetings for comment with no lead time allowed for preparation. He somehow found time to review the material and give us insight into those mandates most critical for us to address.

I will always remember the long car trips to outlying county medical societies when the two of us could discuss the traits of that society to help me prepare to understand them, help them, and represent ArMA to them.

Whatever was achieved during my presidency of ArMA was enhanced and facilitated by Bruce. He was always on tap, never on top. I would gladly give him a plaque if I could have him back.

Philip E. Dew, M.D.
President, ArMA 1973-74

The C.D. Alternative

Single Premium Annuities are the perfect savings plan for physicians who are dissatisfied with the tax status and yields on their C.D.s.

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Annuities are a favorable alternative to C.D.s because the value of compounded interest, on a tax deferred basis, over a period of time is very significant. The Tax Reform Acts of 1986 and 1988 preserved the favorable status of annuities and has left them as one of the very few tax shelters still available.

Most insurance companies are currently crediting about 9% interest. Yields in that range will roughly double in eight years.

Taxable C.D.s on the other hand, require about twelve years to double in value, at the same rate of interest (9%), in a combined 33% Federal and State tax bracket.

To further illustrate the value of compounding tax deferred interest, lets assume that a 41-year-old physician invests $100,000 in an annnuity which is crediting 9% interest, and continues crediting 9% interest until he is 65-years-old. At that point, the physicians investment would be worth about $800,000. Meanwhile, his 41-year-old attorney friend rushes to the bank and purchases a C.D. for $100,000. After paying Federal and State income taxes every year, on the interest earned, his investment would actually net him about $405,000.

Annuity interest rates, are guaranteed from one to five years, and early withdrawal penalties range from one to eight years (not unlike C.D.s). Most annuities allow 10% of the values per year to be withdrawn without penalties.

Many companies have "bail-out," provisions. These are actually escape clauses, which allow investors to exit without penalties, if the renewal yield falls one percentage point, or more, under the initial rate guarantee. Other companies do not have these provisions, but rely on their demonstrated performance year after year. All companies do guarantee the principal at all times and have floor rate guarantees of 3% to 5% at all times.

Although Municipal bonds also have tax advantages, they do not guarantee an investor's principal the way annuities do.

Annuities avoid probate, which result in substantial savings to the owner's family. They also provide an income which can not be outlived, if the owner chooses that option.

Annuity values grow faster than taxable savings like C.D.s, because the principal earns interest, the interest earns interest, AND, the interest that would have gone to pay taxes, earns interest.

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Please call me at the ArMA office when your next C.D. renews, or if you are considering buying one now. I will be happy to show you how the C.D. alternative, can provide you with a safe and convenient way to defer taxes, while accumulating wealth.

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Join Us July 1-July 8

At my first Board meeting as a Director of the Arizona Medical Association, the decision was made to have Bruce Robinson as our Executive Secretary.

During my board tenure, due to a change in our bylaws, I was Chairman of the Board for two years.

It was during this time that the availability of professional liability insurance became a problem. We decided to build and own our own headquarters building. We developed a productive and ongoing relationship with the Arizona Legislature.

Bruce Robinson was a positive factor in these matters. He was a very productive administrator and many of the problems of the Association were solved, or made less of a problem, by his astute and intelligent advice and action. Bruce was a major factor in our Association reaching many of its goals and objectives.

We shall miss his helpful and gentle attitude. But most of all we shall miss Bruce Robinson, the man and devoted friend of the members of our Association.

James L. Grobe, M.D.
ArMA President 1971-72

Bruce Robinson replaced Robert Carpenter and continued his excellent programs in a very satisfactory fashion. My memories of him are all favorable.

Robert E. Hastings, Sr., M.D.
ArMA President, 1950-51

Bruce was first known when he started with ArMA in February 1964. This was during my terms as Secretary, and my contact with him gradually became more regular. He was relatively young, eager and able to learn, affable, friendly and accommodating. Over the years a few problems or questions arose, and, while he made the decisions, we discussed the various aspects of the problem.

Bruce became Executive Secretary in January, 1970, during my terms as Speaker of the House. During that time, and since as Chairman of the Bylaws Committee, he was always most accommodating, getting information from other sources, and offering his own input and opinions.

Bruce will be missed because of his various attributes, and he will be remembered for his contributions to ArMA.

Charles E. Henderson, M.D.
Secretary, 1962-67
Parliamentarian

I knew Bruce Robinson for many years in my various officerships in the Arizona Medical Association. He was always knowledgeable about the workings of the organization and about the greater social and economic background against which it operated. His ability to provide relevant information on a multitude of problems was extensive and his responses were always prompt.

Bruce acted in a quiet fashion. He was skilled in seeing that the activities of our organization proceeded without hitch.

I will miss his guiding presence at ArMA.

Robert S. Hirsch, M.D.
ArMA President 1987-88

Bruce came to work for our Association the last year that I was Speaker of the House. Bob Carpenter was Executive Secretary then, and Bob and the Board were enthusiastic about the new Assistant Executive Secretary that we knew would one day serve the Association with distinction. And indeed he did, becoming a few years back, President of the American Association of Medical Society Executives.

Bruce was a quiet man, courteous, efficient and accommodating. His knowledge of the affairs of the Association and national organizations was broad. He never failed to amaze me with information from off the top of his head. Bruce was never too busy to give personal attention to matters that were of concern to the individual. Therein lies the differences between someone who cares, and someone who fills a position. We shall miss his presence at the Association, and many of us shall miss him as a friend.

Paul B. Jarrett, M.D.
ArMA President 1966-67

Some Thoughts About Bruce Robinson

Bruce was a caring, thoughtful influence in my life during the time I was very active as an officer in the Association. He gave me support. He shared his concerns with me. He consistently put the concerns of the Association above any personal considerations. He was able to look with humor on his own foibles and deal with some very difficult situations very gracefully. When I called for his help at about midnight during the annual meeting, when I was president, because I was being confronted by a Pro-Life group who was protesting that they had not gotten booth space, even though they had not applied for it in a timely manner, Bruce came to my room and was courteous, firm and very helpful, and still compassionate to the people who were making unreasonable demands. When we went to a County Medical Society Meeting and were involved in a meeting with a lot of conflict between different members of that society, Bruce was a healing influence and yet was able to see the humor of the situation as we departed. I haven't seen much of him for the last few years, but I feel his loss very deeply.

John J. Standifer, M.D.
ArMA President 1972-73

Bruce E. Robinson — The Man

Bruce Robinson was born May 5, 1927 in Cordelia, California, and, as that town had a legendary rattlesnake population, was early in life imbued with virtues of prudence and caution. Graduation with a University of Washington, B.A. in Business age 24 was followed by marriage age 25 to Betty Jones, B.A. in Nursing from the University of Iowa. Relocation to Anchorage, Alaska ensued, Bruce, now serving as controller for the Northern Commercial Company and the Robinsons becoming friends with neighbor Misty Coumbe.

At age 38 the beauty of Arizona led to employment in the Arizona Medical Association. This was followed by recruitment of Misty and 25 years service, primarily as Executive Director.

Those were the highlights, but what brighter beacons did Bruce leave for those he served -- ArMA, his peers, his family?

The Arizona Medical Association: ArMA is nationally respected, a model of efficient organization. Its annual meeting, meticulously detailed from House of Delegates and guest speakers to the location of every exhibit -- its committees' service to members, its handsome headquarters, all were a shared product of Executives, Directors and -- Bruce. ArMA, truly professional in function thus remains in the hearts of every officer, physician, and staff member as a lasting memorial to Bruce Robinson.

To his peers; and most especially to every ArMA president, Bruce served as an advisor, wise counselor, a rock in any storm -- yet always prudent -- seeing that policy decisions were openly presented and voted on by the Board of Directors.

Bruce's election in 1985 as President of the American Association of Medical Society Executives was recognition for long years of service to other Associations. At American Medical Association meetings, he was a figure of respect, providing ready access to Executives and Trustees when requested by ArMA officers.

To his family: daughter Carol, B.A. in music therapy, her career especially in the service of the profoundly handicapped adult. His son, Stanley, M.D., presently serving in the care of Maricopa County indigents, son Jerry, graduate of DeVry Institute, working in the computer industry and California surfer – all three a source of their father's pride and joy.

To his spouse: Bruce was blessed in Betty, not only as loving wife, but also as true friend. They shared careers, everlasting gin rummy, travel and whenever separated, daily phone calls. This soul-friend relationship allowed for an ever deeper spiritual commitment, exemplified during recent years of stress by a program of daily a.m. scripture reading followed by fifteen minutes of shared meditation.

Ask to delineate what manner of husband was Bruce, Betty replied, he was "a private person," restricting all personal problems to their own twosome. He was "gentle, romantic, tolerant, understanding, loving and considerate of other people." Betty then brought forth a plaque kept on his working desk, and asked that it be appended as best summing up the Franciscan type man Bruce strove to be: "Oh Devine Master -- Grant that I may not so much seek to be consoled as to console, to be understood as to understand, to be loved as to love. -- For it is in giving that we receive, it is in pardoning that we are pardoned, and it is in dying that we are born to eternal life."

Bruce Robinson, we thank you for your vocation of service, your dedicated family life and your friendship. For now, Vaya Con Dios and -- a brief farewell!

Earl J. Baker, M.D.
ArMA President, 1984-85

There are two ways of knowing a person. Through friendship, which is by far the most rewarding, or through one's reputation, which of course is reflected in his family, his faith, his manners, to his earthly accomplishments and contributions.

God blessed Bruce with an abundance of human qualities which invited friendship and accorded him many talents which he used to serve his fellow man.

I am one of the many fortunate persons who considered Bruce a friend and a gifted colleague since my earliest days in the association field. In the last dozen or so years, we had numerous occasions to work together on board and committee projects in behalf of medicine and our own professional association. I must admit that frequently, I would quietly admire, if not outright envy the quiet leadership which Bruce always seemed to bring to the various forums. He didn't pound the table, he rarely criticized a fellow executive or a divergent point of view, but most often ended up on the winning side of a debate or discussion. His experience and courteous manner were the factors which no doubt were his greatest strengths. His commitment to medicine and his members was without question.

Like many hundreds of his associates, I am going to truly miss my friend. I suppose that for a little while at least I will look for him at an AMA or AAMSE meeting until the habit subsides. But I will not forget him. Indeed, I hope to even enjoy some of the fond memories and still use some of the advise which he left me.

James R. Hickox,
Executive Director,
Harris County Medical Society,
Houston, Texas

My life as a medical society executive was better for having known Bruce Robinson. He was a friend, a respected colleague and "stood tall" as a leader among his peers.

With a twinkle in his eye he was ever willing to share his expertise with fellow executives. While he did an outstanding job whenever he made a formal presentation, he was at his best in a "one on one" discussion or problem solving situation. Raising the education level of medical society staff members was serious business to Bruce.

His personal advice was good too--like when one might bemoan some circumstance of your current employment to which Bruce would typically reply "have you ever thought about working harder to make your situation a better place to work?"

Prior to my retirement as Executive Director of the North Carolina Medical Society, Margaret and I naturally saw Betty and Bruce several times a year at AMA meetings, Medical Society Executives meetings and Professional Convention Management Association meetings.

As serious as he was about business, there were still fun times. A shared drive along the northeast shore of the island of Oahu or a visit to the Texas LBJ Ranch.

I guess you know by now how I felt about him. One is never quite ready to give up a friend. Thank goodness we have the good memories.

With kindest regards

William N. Hilliard
Retired Executive Director
North Carolina Medical Society

Bruce Robinson was known to me as a good and admirable friend.

I shall always remember him as a big man, with a gentle smile, a firm handshake and eyes that looked directly at you in conversation.

In demeanor, he was always a gentleman. He was not reluctant to express his views and positions on issues, but he was never obstreperous or obstructive in doing so.

Bruce was the kind of association executive that most of us aspire to be. He attained the position of President of the American Society of Association Executives by virtue of his knowledge, his foresight, and his leadership abilities.

As fellow association executives, Bruce and I had a friendship that revolved around medical society meetings. I often enjoyed his company at both the conference table and the dinner table. He never imposed himself on anyone; on the contrary, I--and others--naturally gravitated toward him.

I liked and respected Bruce Robinson and feel very privileged to have known him. I wish I had known him better.

Eldon E. Huston
Executive Vice President
Iowa Medical Society

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I met Bruce Robinson shortly after his being hired by ArMA. He had been a hospital executive in Anchorage, Alaska.

An early accomplishment was working with Editor Rollie Shoen, M.D., of Casa Grande and completely reworking *Arizona Medicine* and raising it to national award-winning status.

In 1968 ArMA Executive Robert Carpenter was approaching eligibility for retirement. At the end of the 1968 annual ArMA meeting, the Board of Directors convened and Bruce was elected to take over Bob's duties.

The first major accomplishment was the funding and building of the present headquarters. On a regional basis the Rocky Mountain States joined forces and became a "political voice" at the AMA level. This led to the election of Dan Cloud, M.D., of Phoenix as President of AMA. The State of Arizona became a forerunner in many areas because of Bruce's involvement in MICA, BOMEX issues, etc.

I could fill pages with Bruce's accomplishments but what stands out most in my mind was his gentle ways, never complaining and always available to help in a crisis. Perhaps he gave too much. Bruce lived by the words of Rudyard Kipling's "IF." He took care of the most mundane matters--even to making coffee on weekend morning meetings. He made our work more carefree and I will always miss this gentle man--but will be proud that I can remember him as MY FRIEND.

Arthur V. Dudley, Jr., M.D.
ArMA President 1968-69

A Tribute to Bruce Robinson

Gentle and soft spoken he was. The smile which danced in his eyes revealed the warmth of his love for those who shared his world.

This is how Bruce Robinson appears when his image comes into focus. This is how I will see him for as long as I live.

Jean and I always looked forward to seeing Bruce and his wife, Betty, at the meetings of the American Medical Association and of the American Association of Medical Society Executives.

Once we explored with them the coastal cities of the Ante-Bellum South, Savannah, Charleston and Beaufort. The trip was memorable in many ways, but what made it most pleasant was being with these two people, whose sunny dispositions and natural goodness won for them a special place in our hearts.

Hart F. Page
Retired Executive Director
Ohio State Medical Association

Bruce Robinson was a professional colleague and trusted friend.He was the best of both, and will be missed deeply by all who worked with him and shared his friendship.

I began my tenure as a state (Washington) Medical Association Executive Director shortly after Bruce replaced Bob Carpenter as the Exec in Arizona.

We new execs met in Phoenix during the Spring of 1973. This was a COWSMAE (Conference of Western State Medical Association Executives) meeting. I was greatly impressed with Bruce and his quiet demeanor, yet firm grasp of the issues and how you build a consensus within leadership to move an Association in a positive direction.

It was at this meeting that I first got to know Betty Robinson. I had always placed Bruce and Betty Robinson on a pedestal of what a marriage should be. A highlight of attending national or regional meetings was a chance to go for a walk or have dinner with Bruce and Betty and talk about "our" world of Association Management and it's impact on "our" lives.

Between 1973 and 1986, when I quit the WSMA, I talked with and stole from Bruce ideas and strategies on resolving the liability problem, the role of the Association in implementing the PSRO, the involvement of medical students and resident physicians within organized medicine, running a "favorite son" for trustee and president of the AMA, keeping physicians ahead of health planners, implementing CME accreditation programs and working with impaired physicians.

We will all miss Bruce Robinson and we will all remember him as a cherished friend, and respected colleague.

Harlan R. Knudson, CAE
Executive Director
Washington State Medical Association
1973-1986

I first met Bruce Robinson in 1964 when he came to work for the Arizona Medical Association. To use a hackneyed phrase, those were simpler times, at least in Arizona. The offices of ArMA were on the second floor of the UR building at 4533 N. Scottsdale Road, adjacent to the Safari Hotel, and there were few employees. Bob Carpenter had been Executive Secretary for many years and also served as Executive Secretary of the Board of Medical Examiners (BOMEX). On board as Assistant Executive Secretary was Paul Boykin, when Bruce was hired as Executive Assistant.

With the growth of the population of Arizona and the increase in the number of physicians, a decision was made in 1965 to divide the duties of the two assistants, so that Paul spent most of his time with BOMEX and Bruce concentrated on ArMA. For a few years thereafter both men were paid in varying percentages by both organizations, but eventually the tie was completely broken.

As the 60s drew to a close, plans were drawn for a new Association headquarters which we now occupy, and Bruce was a strong force in the design and furnishing of the new building. Having been appointed Assistant Executive Secretary in 1965, Bruce became Executive Secretary in 1970 upon the retirement of Bob Carpenter, and Paul Boykin succeeded to the same position in BOMEX. Finally in 1983, the Board changed Bruce's title to Executive Vice President.

Over the years Bruce Robinson consistently demonstrated his executive abilities as well as his ability to get along with us doctors. There was never any evidence of favoritism towards any of his physician employers. He worked quietly and efficiently to carry out the policies set by the Board of Directors, expanding the staff and scope of the Association as the membership grew. He never tried to set or influence policy but was always present to see that everything was accomplished. Besides being present on his job daily, he spent countless evenings and weekends attending committee meetings and other functions.

Although these activities would seem to have required time and a half of any man, Bruce had the capacity for other accomplishments as well. During the hectic days of the special session of the Legislature on medical malpractice in 1976, Bruce worked day and night with Jack Brooks and other members to secure passage of significant legislation. He had been instrumental in bringing the Travelers Insurance Company to Arizona in 1971 to provide a state sponsored program. When they abruptly announced their departure, initiating the crisis of availability of insurance which led to the special session of the Legislature, Bruce was again instrumental in rapidly accomplishing the financial measures needed to effect the establishment of the newly authorized doctor-owned and ArMA sponsored company, MICA. Subsequently, Bruce became the only non-physician member of the Board of Directors of MICA and served as Treasurer of the company until his death. It was always a little amazing to me how well he understood and could answer any questions about those complicated financial statements presented monthly at the MICA Board meetings.

AMA activities always seemed to be a favorite part of Bruce's duties with ArMA. He attended all House of Delegates sessions and managed the responsibilities of our delegation superbly. Together, he and Scott Chisholm, with the help of the rest of the delegation, put together a magnificent political campaign which resulted in the election of Dan Cloud as President of the AMA and the sight of dozens of AMA delegates parading down Michigan Avenue's Magnificent Mile in Chicago in Arizona cowboy hats. Through his association with other medical society executives at the AMA he became a member of, and subsequently President of the American Association of Medical Society Executives. His opinions and leadership were always highly respected by his peers throughout the country.

Bruce Robinson was a quiet man. He had a successful marriage and raised three children to be proud of, one of whom is now a physician practicing in Phoenix. He always seemed to maintain an even demeanor and never discussed any personal problems with us, although he certainly had his share of them. He was always available, always efficient and always pleasant. If there is one phrase that always proved true and that I'll always associate with Bruce, it is "I'll take care of it." He will be deeply missed by many.

Ed Sattenspiel
ArMA President 1976

Bruce Robinson was Executive Director of ArMA for almost nineteen years, and was an Assistant Director for some six years before that. I grew up in the Association with his help, and he always made my job easier. It didn't make any difference whether I was a new member of some obscure committee or President of the Association. His information was always current, correct and willingly given.

Past Presidents are a group of individuals, none of whom like to agree with other members, but all who have worked with Bruce agree that he made their job easier, made them look good, giving them the credit when he did most of the work.

Thanks to the dedicated work of Bruce as Executive Director, ArMA is better able to support the physicians of Arizona in the multiple problems we now face.

Richard O. Flynn, M.D.
President, ArMA 1969-70

Of Our Friend Bruce . . .
A Sad Goodbye - A Fond Memory

"And now the time has come when we must depart. I to my death - you to go on living, but which of us is going to the better fate is unknown to all except God." anonymous

All of us were shocked and saddened by the untimely death of our colleague and friend Bruce Robinson. We all, I am sure, share with his family the despondency of heart and spirit caused by the loss of this fine gentleman. It was my personal pleasure to know and work with Bruce in the many activities of the American Association of Medical Society Executives. Bruce earned the respect of his colleagues for his demonstrated unselfish commitment to the physicians he served as well as the standards of excellence he sought and worked for for AAMSE. Quiet efficiency marked his year as President and spoke well of the character of this mild mannered man who never sought personal recognition but instead constantly extolled the accomplishments of all those around him.

Death has taken a fine friend from us but memories bare eternal smiles for the living.

Donald C. Jones
Executive Vice President
Florida Medical Association

"Greatness in man is in proportion to the size of a problem that it takes to get his goat."

To most of our Arizona physicians the name of Bruce Robinson brings up an immediate relationship with the Arizona Medical Association, for in the memory of most of our members Bruce Robinson has directed our efforts on the state level. For over twenty-five years Bruce has been our Executive Director and has arranged or supervised most of our activities. Throughout this span he has handled all the cancelled appointments, met all the unseen emergencies and remedied all the "glitches" easily and efficiently.

The many meetings of our Board of Directors have always been well planned by Bruce. The proper information has been reproduced and made available. Attendees have been formally invited and facilities for their comfort assured. The many committee meetings our large Association has required have been efficiently arranged and no detail forgotten. Appropriate refreshments have always been available to make our duties smoother and more enjoyable.

The all important annual meetings of our House of Delegates and those of our membership at large have always been planned to the last detail. Appropriate seating arrangements have been provided, microphone needs installed and proved effective, transcription services for our reference committees have been obtained, timely bulletins always provided, necessary prompting for the Speaker of the House of Delegates has been available when required and a pleasant atmosphere has prevailed.

Through it all Bruce has been there, smiling with reassurance and confident that all was in readiness. If anyone--officer or member alike--needed information or additional equipment Bruce knew how to provide it or arrange for it. He was always available and so pleasant during these important, and at times, hectic gatherings, all of which lent prestige and confidence to our Association.

To say he will be missed is a gross understatement. How can ArMA go on without Bruce? I am sure it will, but our adjustments will be painful and the transition precarious. What a great asset he has been for this quarter century to all of us in the Arizona Medical Association.

Robert A. Price, M.D.
Speaker of the House 1972-88

The measure of our grief is the measure of our affection and respect for Bruce. I still have not recovered from the shock of his loss to us, nor the pain that still remains. He was much more than a highly competent professional at his work, more than one who held high respect from his colleagues. He was also a good friend, a kind and thoughtful person who was quick to respond to the needs of others. I cannot count the times he came to my rescue with assistance with my problems as a medical executive. His quiet reassurance and support were always there when it was needed. It has been a friendship which I will always treasure.

Don W. Sower
Executive Director
Idaho Medical Association

Mentor, advisor, teacher, friend--these, and many other words, are only paltry expletives when applied to the person of Bruce Robinson.

Over the years, Bruce was truly all of these things to me. His sound advice and reasoned council was of immeasurable value to me on many occasions. With Bruce's guidance, and many other people's help, ARMPAC developed in it's formative years into a potent force on the Arizona political scene. During the years that I served on the Executive Committee, Bruce's quiet leadership kept the Arizona Medical Association's ship of state well on course. His ability to so adequately and precisely present all of the facets of intricate problems made solutions readily possible to me during my year of Presidency. Bruce had the firm conviction that decisions on behalf of ArMA had to be made by the president. He never strayed from that course when at times he could have quickly made an executive decision on his own. For that, he has had my undying respect.

For his kindness, understanding, integrity, and loyalty, Bruce Robinson will always be remembered as a Man among men.

John F. Kahle, M.D.
President, ArMA 1977-78

Fairness and integrity of confidentiality are the two qualities exemplified by Bruce Robinson in his executive role during my five years of active leadership involvement with ArMA.

A retrospective view of the personality types, coming as it were, in battle armor into the leadership of ArMA, and how each was dealt with successfully by an enduring executive can only be described as an amazing improbability, yet it happened--like a wise mother dealing with her flock of young. And like a mother, there was caring for family--the medical family--and I mean all of the medical family. Sometimes with a gentle opacity of his response to the issues of current concern. Time has brought clarity to this, best exemplified in a word--fairness.

His capacity for maintaining a confidence of intent in his interrelationship with ArMA leaders would be a worthy virtue for us all to shoot at. His successful achievement in this speaks only too clearly of the gentleness in his character and simple absence of meanness in his nature.

In his absence, I will be forever reminded of the frailty of the human existence.

Clyde W. Kurtz, M.D.
ArMA President 1981-82

I knew Bruce before he was "the boss" and always found him responsive. Before I became involved as an officer I had concerns that proved to be completely unfounded regarding his commitment to ArMA.

The man was a tireless, dedicated worker and leader during my high activity years of 1980-84, and handled the position of dealing with many and constantly changing Presidents as if he were made for the job. He also grew in stature and was able to utilize the quality of hiring and keeping top associates. He worked hard, but learned to delegate appropriately, and usually even smiled with the tough times.

I shall certainly miss him.

John Oakley, M.D.
President, ArMA 1982-83

Bruce Robinson was and always will be remembered by myself and my family as a true friend. He has guided me through the highways and byways of Arizona medicine. I could not help but remember vividly when I was elected as Treasurer of ArMA, when after the first Board of Directors meeting, he generously offered his help in my transition from a dues-paying ArMA member to being the newest member of the Executive Committee.

His wealth of knowledge was readily available and fully given to me during my stewardship of the finances of ArMA. He has shown understanding and knowledge of how we can best accomplish the function of ArMA to its members in the most cost-effective way.

During my year as President of ArMA, his counsel and advice were well thought of, and my relations to staff made pleasant by his guidance. I was able to establish what I believe was a good rapport with our legislators through his advice. My goal of making every member of ArMA, especially the outlying counties, an important part of the State organization was cultivated and nurtured with his invaluable help.

Above all, he was a friend among friends, and we will miss him.

Pete Robles, M.D., Tucson
ArMA President, 1983-84

I only knew Bruce for a moment in the vast time of life, and yet I feel the numbness in the aftermath of his death and the loss of a friend.

I first met Bruce Robinson in 1977 when I started working for the Board of Medical Examiners (BOMEX) as its Associate Director. BOMEX was housed in the ArMA building so I was introduced to Bruce within the week. I remember categorizing in my mind that the ArMA Director was a quiet giant--he sure was a lot taller than me. Bruce appeared to be cut from the traditional executive stock, keeping his cards close to his vest, keeping his thoughts to himself and probably not even eating quiche. However, there was a warmth behind Bruce's exterior that one could feel in his smile, his voice and laughter. And though he seemed to tower over my 5'10" frame, he communicated with me at a level I could grasp.

Bruce's sensitivity and abilities as a "people person" was first recognized after I was invited to attend a party in Tucson. I showed up in my best corduroys and knit shirt with a six-pack of beer tucked neatly under my arm only to be greeted by one of the tuxedoed caterers. I then looked up and saw that the men wore three-piece suits and the women were clad in evening gowns. My confidence was shot as I thought, "what have I done?" It seemed to me that every eye was staring at me and I didn't recognize one face as I quickly took inventory of all the guests. Then this big hand came down on my shoulder. My mind raced, wondering if this hand belonged to the bouncer who was about to throw me out, or show me to the pool which, perhaps, needed to be cleaned. A gentle voice greeted me and Bruce began to introduce me to a group of physicians and their spouses. I quickly related my story of embarrassment only to have Bruce and the others tell me of similar events in their lives, of faux pas at parties they had attended. Through the laughter and stories, I felt accepted and no one probably remembers the party incident but me. I knew that my saving friend created a foundation for a professional relationship that strengthened over time.

Our conversations allowed us the opportunity to know each other better, as well as the ever changing personalities of the organizations we supported. The net result was that we learned how ArMA and BOMEX could more effectively work together and where differences could be addressed in a healthy and challenging manner. To Bruce's credit, he never asked for "inside" information about an investigation being carried out by the Board, and even more importantly, he never once tried to influence the outcome of the Board's deliberations.

I believe that Bruce and I realized that as BOMEX became independent, both the goals of the state agency and the state association were often similar, even if we chose different ways to carry them out. I have always strongly believed, and Bruce concurred, that if BOMEX carried out its legislative mandates, the public would be served and the profession strengthened even when physicians were disciplined, rehabilitated or even removed from the practice of medicine when warranted.

During the eleven-plus years of my association with Bruce Robinson, I never saw him display anger or speak with malice toward anyone. Bruce had a tremendous ability to contribute to the successes of others while never requiring the limelight.

The quiet giant made a personal decision to end his life; a decision in which he asked for no support or a vote from anyone or any group. The decision was personal and not made to hurt the people who crossed his path. I choose to remember Bruce for his support and wisdom, his humor and advancements, and his efforts to balance the complexities and frailties of life.

Perhaps now is the time to think about Bruce in relationship to a short prayer which may assist us in pursuit of our daily endeavors, and the need to let some things be.

God grant me the serenity
To accept the things I cannot change,
The courage to change the things I can,
And the wisdom to know the difference.

Doug Cerf
Executive Director
Board of Medical Examiners

Bruce Robinson was a true gentleman, an outstanding medical society executive, a dedicated family man, and a wonderful friend. Those of us who had the opportunity to work closely with him quickly grew to appreciate his quiet demeanor, deliberate analysis and wise counsel. He was dedicated to his job and family and contributed immeasurably to both.

Medical executives have lost a valuable asset and friend. We mourn his death; he will be sorely missed and long remembered.

David Bickham
Executive Director, Oklahoma State Medical Association

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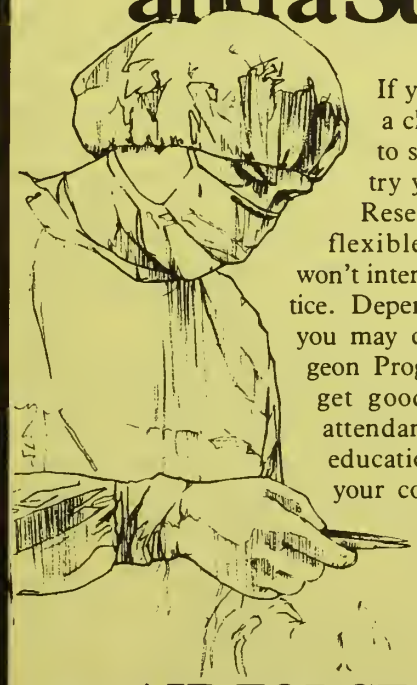

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A GREAT WAY TO SERVE

Since Bruce and I both go back for over twenty five years with our respective state medical associations, and served together going through the chairs of AAMSE and PCMA, we obviously could not escape firming up an excellent and lasting relationship.

I always had tremendous respect for Bruce and his feel and knowledge of the medical association business. First he looked the part, distinguished and reserved, but authoritative. Secondly, he was rather quiet (not running off at the mouth all the time, for sure) but when he did speak, he made significant contributions to the group. We listened. I always seemed to reserve my greatest respect for people like that. Bruce Robinson always received my respect, and he knew it. When I didn't know where to turn, I often called him.

Because of his contributions to us individually, our executive oriented organizations, and especially medical associations and the medical profession, he will not be forgotten. To the contrary, his dedication and commitment will live on through all his past fellowship with his peers and friends who continue the task at hand.

Robert G. Cox
Executive Vice President
Kentucky Medical Association

Tribute to Bruce Robinson

I will miss Bruce Robinson--gracious, supportive, knowledgeable, professional, quiet yet impressive, the perfect host, a good friend. Bruce was my next door neighbor, so to speak. He was the one I called upon most for advice, help or support. He always came through, and always with much more than I asked for or expected. He visited Utah more than any other medical exec, not through obligation but friendship. When I asked for an Arizona speaker for a recent Rocky Mountain Leadership Conference, he not only arranged for the best but picked up the expense of a chartered plane to bring him here. That was Bruce to me. Gracious, yet much more, a true friend.

J. Leon Sorenson
Utah Medical Association

As an old-timer still active in medical association administration, it has been my privilege and pleasure to be a friend of Bruce during all of his career with the Arizona Medical Association, and I know of no one more universally highly respected and esteemed by his colleagues than he.

His leadership capabilities, his effectiveness in his work, his gentle and polished manner, his integrity and his charm endeared him to us all. His passing leaves a tremendous void in our ranks, for he truly was one of God's Noblemen. Sadly, he was a casualty of his dedication to his profession.

I was chairman of the Nominating Committee of the Professional Convention Management Association when Bruce was unanimously elected a member of the Board of Directors, where he again quickly demonstrated his great capabilities. I am sure that ultimately he would have become President of that organization, thereby to become one of a very small number of executives who have served as President of AAMSE and PCMA.

We will miss you, Bruce, beyond measure and without end.

Harold W. Brunn
Secretary-Treasurer
North Central Medical Conference
St. Paul, Minnesota

Bruce Robinson, A Dear Friend

I always looked forward to seeing and visiting with Bruce Robinson, because he was a close colleague and dear friend.

He was more than a fellow state medical society CEO. Bruce was a counselor and advisor. He could always be counted on to listen and to offer a perspective--one that brought reality into focus.

He enjoyed his work. He loved his wife and family. He cherished his many friends.

I recall his unannounced visit to my office in Portland while he and Betty were vacationing in the Northwest during the early 70's. He was aware of the turmoil I was going through legislatively over a controversial issue which had a number of ministers hounding our office. Demonstrating a sly bit of humor, he presented himself to our receptionist as, "The Very Reverend Robinson," and said he wanted to see me on a matter of great and urgent importance. "No, tell him I'm tied up and cannot be disturbed," I begged. "Not good enough," claimed The Very Reverend Robinson. "I demand to see him now!" What a relief it was to discover a friend.

To say that we in medical society management will miss Bruce is an understatement. He was a genuine human being, and his warm influence and gentle manner will long be a part of us all.

For me and others in medical society management throughout the country, and for all of you in his home state, a dear friend is gone. But what Bruce Robinson of Arizona stood for lives on.

Robert Dernedde, CAE
Executive Director
Oregon Medical Association

Physicians In The News

Mehernaz Irani, M.D.

Easter is going to be a brighter time for needy Casa Grande children when **Mehernaz Irani, M.D., F.A.A.F.P.** and her husband, Noshir, host "Hop, Skip and Jump into a Child's Heart," which will be a pancake breakfast at her husband's restaurant for children whose families are financially distressed.

The breakfast is a continued effort to assist with the Casa Grande Adopt-a-family program, of which Dr. Irani devotes much of her time.

Dr. Irani has been involved with the Adopt-a-family program since its inception, and has helped Ruth Haywood, who organized a community drive several years ago to assist families in need. A meal is prepared at Thanksgiving for those who have nowhere to go for the festive meal.

"Just because we are physicians doesn't mean that we should be all wrapped up in our practices. I feel we should do things for community members," Dr. Irani said.

A family practice physician who has been in practice in Casa Grande since 1976, Dr. Irani is one of the directors at the Casa Grande Clinic.

"We really help these families all year round with the Adopt-a-family program," Dr. Irani said, noting that there is always a need for clothing and assistance for local families.

Dr. Irani is a civic-minded individual who became a charter member of another community organization.

Against Abuse, Inc., when it was perceived as a community need for persons who needed a safe environment to go to in the case of domestic violence.

A busy woman, Dr. Irani was named Outstanding Woman of the Year for Arizona in 1984 and was listed in Who's Who in Arizona in 1982-1983.

She is a preceptor for the University of Arizona, has been the chairwoman of the continuing medical education workshops sponsored for the medical staff at Casa Grande Regional Medical Center, participates in the annual Well Person Seminar sponsored by the medical center, is involved with the Arizona learning Disability Chapter and founded the Lupus Chapter in Casa Grande.

She graduated from Girton High School and from Grant Medical College, both in Bombay, India. Dr. Irani performed an internship and residency in family practice at Mercy Hospital in Denver, Colorado and obtained the degree of Fellow of the American Academy of Family Practice in 1981.

Dr. Irani is board certified in Family practice and is a Diplomate of the American Academy of Family Practice. She is a member of the Arizona Medical Association, the American Women's Medical Association, the American Medical Association and the American Academy of Family Practice.

Dr. Irani is dedicated to the principal that it is in giving that we receive.

The first year that Haywood put on the community meal, Dr. Irani and her mother, Goolnar M. Shroff and Dr. Irani's children Anaheeta and Rahzin, helped serve the meal. Her husband, Noshir, is very supportive and they work together as a team. The two believe in a strong, safe and happy family unit and wish everyone could have that.

As a result of her involvement, Dr. Irani is one of the community members quoted in a December *Time* magazine article concerning the community action. She was also interviewed by "Voice of America" radio program.

As she says in her article, "We're doing so much for the rest of the world, but we forget that we have problems right on our own doorsteps."

Edward L. Shaw, M.D., Chief of Ophthalmology at St. Lukes Medical Center recently addressed the Twenty-Second Annual Meeting of the American Academy of Ophthalmology in Las Vegas, Nevada, where he spoke on "Corneal Transplant and Anterior Segment Surgery" and Current Trends in Contact Lens Management, "Therapeutic Indications and Modes of Action."

Dr. Shaw was also seminar chairman for Frontiers in Ophthalmology which was held at the la Posada Resort February 9-11.

My Friendship with Bruce Robinson

It was my pleasure to have known Bruce for the last 15 years of his professional life. I always found him ready to provide information and advice when asked.

He always impressed me as someone who was even tempered and seemingly unflappable. Obviously, he must have had his problems but he never let on. Perhaps for this reason his sudden death was such a shock for many of us. He was regarded as an "elder statesman" by his fellow medical executives, having served as AAMSE President and as a member of the advisory Committee to the Executive Vice President of the American Medical Association.

Several years ago my wife, Frances, and I found ourselves on a Caribbean cruise with Bruce and Betty. We spent over a week together and got to know them well. They were delightful to be with and were largely responsible for the wonderful time we had. Whenever we saw them at AMA meetings in recent years, we would talk about that vacation cruise.

Don Foy
Executive Vice President
Medical Society of the State of New York

Tribute to Bruce Robinson

In 1976, soon after my entry into the medical association arena, the late Bob Lang, then the Executive Vice President of the Cleveland Academy of Medicine, introduced me to Bruce. During these over-twelve-years, I looked up to Bruce as one of the leading medical executives in the country. Many times I've called him on the phone for his advice and consultation. He was always one to share and mentor a young fledgling medical executive. I'll never forget the several times I talked to Bruce about the Colorado executive director job and his fine consultation.

I have many fond memories of the special social times I had with Bruce and Betty. I especially remember the evening in St. George last year at the Rocky Mountain States Leadership Conference western hoedown. We had so much fun together. I have many fond memories of Bruce. I'm sure these memories, his consultations, and listening ear will always be there. I miss him a lot.

Harold Frye
Executive Director
Colorado Medical Society

Bruce Robinson was a gentleman. He was loyal and dedicated to his wife, his family, his job and his friends. I am privileged to be counted among his many friends.

I knew Bruce Robinson for most of our twenty-five plus years of working for our respective state medical associations. It was not, however, until we began serving together as members of the Board of Directors of the American Association of Medical Society Executives and later during his tenure as President of AAMSE, did we become close friends. We also served together as members of the AAMSE Advisory Committee to Dr. James Sammons, Executive Vice President of the American Medical Association and most recently as members of the Board of Directors of the Professional Convention Management Association. As a result of these professional association relationships, I had the opportunity to observe as well as personally benefit from the wisdom and steadying influence Bruce Robinson brought to these important positions and assignments.

As a close, personal friendship developed between us, we found time to visit in each other's home and we shared a wonderful vacation together on a cruise ship to Alaska a few years ago. Having spent some of his earlier years in the majestic beauty of Alaska, the return had special meaning to Bruce as well as Betty who shared his love and fondness of our beautiful last frontier. Last year my wife Elaine and I spent 15 wonderful and unforgettable days in New Zealand and Australia with Bruce and Betty.

Soft spoken, I never observed a time or occasion when Bruce raised his voice against any person. I never heard Bruce Robinson utter an unkind or uncomplimentary word about any individual--physician, layman or fellow medical society colleague. Bruce Robinson didn't have to raise his voice to make or emphasize a point during a discussion. His keen intellectual mind, his ability to see through a controversial matter to reach a logical conclusion was a trait of Bruce Robinson I have seldom seen exhibited by any other individual.

As evidenced by the recognition and tributes bestowed upon him by members of his professional societies and associations, Bruce Robinson was a leader. Walt Lippman said "The final test of a leader is that he leaves behind him in other men the conviction and the will to carry on." Bruce Robinson was such a person. Bruce Robinson was a gentle man.

L. Hadley Williams
Executive Director
Tennessee Medical Association

New Members

The Arizona Medical Association welcomes the following new members:

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Maricopa

Gary M. Boelling, M.D.
Internal Medicine, Geriatrics
13041 N. Del Webb Boulevard
Sun City
Washington University School of Medicine - 1963

Ann Bullington, M.D.
Ophthalmology
367 E. Virginia, Phoenix
University of Arizona
College of Medicine - 1984

Bruce C. Davis, M.D.
General Surgery
1920 E. Baseline, Tempe
University of Illinois
College of Medicine - 1978

H. Gordon Deen, Jr., M.D.
Neurological Surgery
13400 E. Shea Boulevard
Scottsdale
University of South Alabama
College of Medicine - 1978

Edward G. Dolezal, M.D.
Ophthalmology
9221 N. Central Avenue, Phoenix
University of Illinois
College of Medicine - 1983

Janice A. Donnelly, M.D.
Obstetrics & Gynecology
4545 E. Shea Boulevard
Phoenix
Mt. Sinai School of Medicine of City University of New York - 1982

Mark B. Dubiel, M.D.
Psychiatry, Clinical Pharmacology
632 S. 72nd Street, Mesa
University of California
Los Angeles School of Medicine - 1982

Leonard S. Girsh, M.D.
Allergy
3800 E. Lincoln Drive
Suite 26, Phoenix
Jefferson Medical College
Thomas Jefferson University - 1951

Karl A. Hendrickson, M.D.
Anesthesiology
2950 N. 7th Street, Phoenix
University of Arizona
College of Medicine - 1983

Pima

Roger T. Grimes, D.O.
Orthopedic Surgery
3950 N. Campbell, Tucson
Kansas City College of Osteopathy & Surgery - 1967

Michael R. Jerman, M.D.
Cardiovascular Diseases
5402 E. Grant Road
Suite J-1, Tucson
University of Arizona
College of Medicine - 1982

W. Horace Noland, M.D.
Neurology
6636 E. Carondelet, Tucson
U of A College of Medicine - 1984

Associate

Maricopa

James A. Taylor, M.D.
Specialty not available
P.O. Box 5177, Scottsdale
St. Louis University
School of Medicine - 1946

Pima

Stephen E. Copp, M.D.
Anesthesiology
6071 N. Paseo Zaldivar, Tucson
Dalhousie University
Faculty of Medicine - 1952

James S. Hunter, Jr., M.D.
Obstetrics & Gynecology
1818 S. Camino del Sol
Green Valley
University of Maryland
School of Medicine - 1941

Resident

Maricopa

Bhai Dyal S. Khalsa, M.D.
Internal Medicine
P.O. Box 5099, Dept of
Internal Medicine, Phoenix
State University of New York-Buffalo, School of Medicine - 1986

Scott N. Sheftel, M.D.
Internal Medicine
1111 E. McDowell Road
Suite LL-2, Phoenix
Medical College of Ohio - 1988

Pima

Elizabeth A. Grosen, M.D.
Obstetrics & Gynecology
Arizona Health Sciences Center
OB/GYN 8406, Tucson
University of Washington
School of Medicine - 1984

Student

Pima

Skye D. McDonald
3001 E. Drachman, Tucson
University of Arizona
College of Medicine (1992)

While sadness remains in our hearts on his loss, the many contributions of Bruce Robinson stand as a memorial to him. Bruce was a leader in our field.

His perception of issues, his astute evaluation of them, and his thoughtful advocacy of approaches and solutions were characteristics of our esteemed colleague. American Medicine has been well served by his loyalty and his commitment.

Jane and I and medical executives throughout the country have valued the friendship of Betty and Bruce Robinson. We are fortunate indeed that they have come our way.

C. Lincoln Williston
Retired Executive Vice President
Texas Medical Association

Bruce Robinson was a pillar in the medical executive community who was admired and respected by his peers. His leadership style was calm, easy going and guiding. I had the privilege of serving with him on the AAMSE Board and various committees. He was always tolerant of others' views, encouraged everyone's participation as he ensured a fair and productive process for the group to reach a conclusion or resolution. His even tempered nature and gentle, thoughtful manner made it easy to approach Bruce without fear of being judged.

He was recognized for his natural leadership ability throughout his life, yet he didn't seek the spotlight for himself. In his quiet way, he helped develop the leadership skills of younger executives and created opportunities for their achievements and professional growth. His interest and direction in helping others in their professional development and advancing our profession were not well-publicized and sometimes not generally known. His satisfaction seemed to be in the achievements of others. I am grateful for his kind guidance and encouragement over the last few years. I will miss his distinguished and nurturing presence and wish I could have again told him thank you.

Collette Wright, Vice President
Programs and Policy
Los Angeles County Medical Association

I had known Bruce for over 15 years and always did regard him as a most honest, sincere and outstanding individual and without doubt a definite asset to the Arizona Medical Association, its ideals and its goals. Of course, I attended with Bruce many AMA meetings, "exec" meetings, and the Western Physicians Purchasing Association meetings. Bruce's intelligence, foresightedness and leadership were indeed respected and admired by his peers, the other 49 state medical association executives. Bruce's counsel was often sought by his colleagues and his advice most highly regarded and valued.

Bruce Robinson did establish a most exemplary peer role for his colleagues. He will, I assure you, be long and most favorably remembered.

G. Brian Zins
Executive Director
Montana Medical Association

I first met Bruce Robinson when he was employed by Bob Carpenter, the Executive Director of the Arizona State Medical Association.

Bruce and I have shared experiences and information relating to our medical societies on numerous occasions. He was always a gentleman and most willing to be helpful.

We always socialized at various medical meetings throughout the country several times a year. Never have I seen Bruce "out of line" or express a defeatist attitude.

Bruce was my close, respected friend. I grieve over his untimely passing. I and all the other Executive Directors throughout the United States are going to miss Bruce greatly. American medicine has lost a valuable member of its team.

Ralph R. Marshall
Retired Executive Director
New Mexico Medical Society

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Clinical Investigation

Apparent Life-Threatening Prolonged Infant Apnea in Saskatchewan

KORAVANGATTU SANKARAN, MD, FRCP(C); ANNE McKENNA, FRCP(C); MAUREEN O'DONNELL, MD; ABRAHAM NINAN, FRCP(C); GORDON KASIAN, FRCP(C); JOAN SKWARCHUK, RN; *and* WILLIAM T. BINGHAM, FRCP(C), *Saskatoon, Saskatchewan*

Life-threatening events such as prolonged apnea and severe bradycardia are uncommon in infants. When such events occur in a family, however, the results may be disastrous. Over a period of 3 years ending June 1986, we have looked after 111 such infants aged 4 weeks to 40 weeks with a mean age of 14 weeks (male-female ratio 1.26:1). Of these infants, 33 had an identifiable cause and were treated according to the diagnoses. A structural approach to this problem yielded good results. Only 10 infants were treated with a home monitor (4 prescribed by physician and 6 by parental request). Sleep and pneumogram (polysomnogram) studies showed fewer apneic episodes with advancing age ($P<.01$). Giving theophylline seemed to abolish pneumogram abnormalities. No infants died.

(Sankaran K, McKenna A, O'Donnell M, et al: Apparent life-threatening prolonged infant apnea in Saskatchewan. West J Med 1989 Mar; 150:293-295)

Life-threatening events such as severe bradycardia—less than 80 beats per minute—and prolonged apnea—longer than 15 seconds—with pallor, cyanosis, or both are daily events in neonatal intensive care nurseries around the world.[1] Similar apparent life-threatening events are less common in infants aged 1 month to 1 year, but when such events occur in a family, they may create severe physical and neurologic problems for the surviving infant and substantial emotional disturbances to the care givers.[2,3] In the past, physicians tended to approach this problem lightly, particularly if the event had occurred at home and the infant had recovered without sequelae and had normal findings on a physical examination in the office or emergency department.[4] Distressed parents and care givers, however, have resorted to unconventional methods of infant monitoring at home, particularly if, in their perception, physicians seem not to care.[5] Recently, with improved physician awareness, there has been increased attention and understanding given to such problems.[6-8] At University Hospital, Saskatoon, Saskatchewan, we have established an infant and parent support program for such cases. Herein we report the results of our experience over a period of three years ending June 30, 1986.

Patients and Methods

University Hospital, Saskatoon, serves as the tertiary care center for pediatrics for the northern, central, and southwestern parts of the province of Saskatchewan. In this region, approximately 11,000 infants are delivered per year. Over the years a pattern of practice has evolved in which all infants between 1 month and 1 year of age who had an apparent life-threatening event were referred to us for investigation and were seen in consultation by one of us (K.S.). This pattern of practice is such that we are certain that all patients with such events were referred and seen at our center during the prescribed time period. With the help of the government of Saskatchewan and University Hospital, a detailed protocol for investigating and managing apparent life-threatening events was devised and implemented (Figure 1). This involved specialties such as pediatric neurology, cardiology, pulmonology, radiology, clinical chemistry, and social services. Two infants who had been directly admitted to the pediatric intensive care unit with prolonged apnea and cardiorespiratory arrest and who needed mechanical ventilation were excluded from this study.

All infants with apparent life-threatening events were admitted and evaluated in hospital. All underwent a detailed history and physical and neurologic examinations with special attention given to nasal and oral airways.[9] The history included the birth weight, gestational age, and questions for a witness to the event other than the main care giver. Laboratory evaluations included a hemoglobin level, hematocrit, complete blood and differential counts, arterial blood gas determinations, and serum electrolyte, urea, creatinine, calcium, magnesium, and glucose levels. Whenever indicated, specimens of urine, blood, and other appropriate body fluids were collected for culture. Other investigations included an electroencephalogram, chest and neck radiographs, barium esophagogram, electrocardiogram, and, when indicated, two-dimensional echocardiograms. Ultrasound examinations of the head and abdomen were done whenever indicated to rule out central nervous system structural abnormalities and gastrointestinal anomalies. If arrhythmias were suggested, monitoring with a 24-hour Holter monitor was done. Furthermore, all infants underwent an overnight sleep recording that measured respiratory patterns by chest wall impedance, heart rate, and nasal air flow.[10,11]

All infants were attached to an apnea-bradycardia alarm monitor (Healthdyne). The apnea alarm was set at 15 seconds and the bradycardia alarm was set at 80 beats per minute. Apnea was defined as the cessation of breathing for

From the Department of Pediatrics, University of Saskatchewan College of Medicine, Saskatoon.
Reprint requests to K. Sankaran, MD, Department of Pediatrics, University Hospital, Saskatoon, Saskatchewan S7N 0X0, Canada.

longer than 15 seconds with or without bradycardia—less than 80 beats per minute. The overnight tracings were checked for apnea, cardiorespiratory interaction, and variability. Physiologic variability is defined as accelerating heart rate and respirations with movement and during rapid-eye-movement (REM) sleep. Infants in active (REM) and quiet (non-REM) sleep always showed characteristic breathing and heart rate patterns.

As part of a separate study, specimens of blood and cerebrospinal fluid were also drawn from some of these infants to determine β-endorphin concentrations as published previously.[10]

After the evaluation, the infants were subdivided into three groups. Group 1 included infants with identifiable causes, group 2 consisted of infants with normal results on a polysomnogram, and group 3 included infants with abnormal results on a polysomnogram. Group 2 infants and their parents were intensely counseled regarding the normality of results and sent home.

The following criteria were used to identify an abnormal polysomnogram:

- Two apneic episodes for longer than 15 seconds occurred during hospital stay or two episodes of longer than 15 seconds of obstructive, central, or mixed apneas were recorded in an overnight reading.
- A sleep recording showed more than two episodes of apnea for longer than 10 seconds per hour of sleep.
- More than 25% of sleep time was spent in periodic breathing (5- to 10-second apnea).

Group 3 infants were administered theophylline (as Palaron), 2.5 mg per kg body weight per dose three times a day, and the polysomnogram was repeated after 48 hours.[12] All care givers were counseled in detail by one of us (K.S.). Those infants who showed significant improvement after receiving theophylline (no apnea or bradycardia and normal tracing) were discharged on theophylline therapy and advised to return for a repeat polysomnogram in one to two months. If the infants remained symptom free for a month, the theophylline therapy was discontinued and the polysomnogram was repeated. If the results of recordings were still abnormal, the theophylline administration was continued until the results were normal. The use of a home apnea monitor was prescribed only for those infants who showed polysomnographic evidence of apnea even after theophylline treatment. At times it was necessary to prescribe a home monitor for infants whose parents insisted on having one even after adequate counseling. Home monitoring was discontinued in a similar fashion as the theophylline.

Results

No infants died during the study period. No attempt was made to see whether this was statistically significant as the numbers were too small. All infants by virtue of design had a polysomnogram. A total of 111 infants (62 male, 49 female) aged 4 weeks to 40 weeks with a mean age of 14 weeks were evaluated. Group 1 consisted of 33 infants (16 male, 17 female), and they were treated according to their respective diagnoses (Table 1). Group 2 consisted of 34 infants who had normal results on a polysomnogram and normal test results; they and their parents were counseled and sent home. Six of these infants, however, were sent home with a monitor because of parental pressure. Group 3 consisted of 44 infants showing abnormal results on a polysomnogram, and they were assigned to receive theophylline treatment along with counseling. Four infants who continued to have abnormal

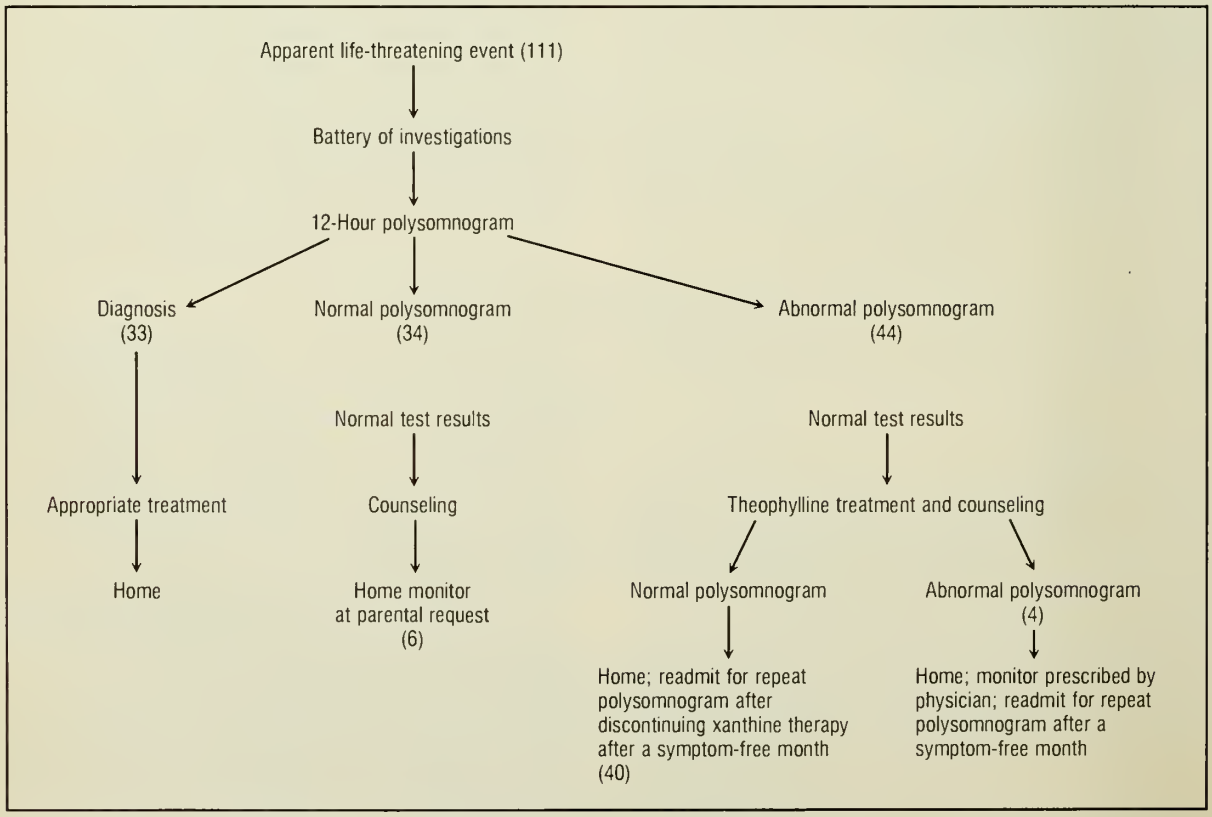

Figure 1.—The flow diagram shows the approach for evaluating apparent life-threatening events, based on experience with 111 infants. The numbers in parentheses represent the number of infants in this study.

TABLE 1.—*Etiologic Classification of Infants With an Apparent Life-Threatening Event*

Diagnosis	Infants, No. Total (N=33)	Male (N=16)	Female (N=17)
Infection	11	4	7
Regurgitation and apnea	6	3	3
Narrow upper airway syndrome	6	4	2
Seizure disorder	5	2	3
Congenital heart defect	3	2	1
Exposure to noxious agent (reflex apnea)	2	1	1

polysomnograms were advised to use home monitors (Healthdyne, Model No. 1690, Marietta, Georgia). The rest of the infants (40) showed improvement with theophylline treatment and were followed up according to the protocol (Figure 1). Only 2 of 111 infants were born preterm and were treated in a neonatal intensive care unit.

Overall, the number of apneic episodes decreased significantly with increasing age ($P<.01$). The number of apneas per ten hours of tracing were 12.4 ± 2 at 4 weeks, 5.6 ± 1.5 at 12 weeks, and 1.5 ± 0.5 (mean $\pm$ standard deviation) at 24 weeks of age.

Ten infants (eight male, two female) were treated with a home monitor. Four of these infants were from group 3 and 6 from group 2. The care givers who used monitors at home felt that it was worthwhile having the monitor even though false alarms were frequent. Regardless of the group, the parents of infants who went home with a home monitor were given detailed instruction in the cardiopulmonary resuscitation of infants and neonates using a structured protocol. Facilities were also made available for maintaining the equipment. All monitors prescribed were supplied by the program and required a monthly fee of $120. The home monitors were capable of both high and low alarms for heart rate and apneic periods of 10, 15, and 20 seconds.

Discussion

This is a detailed report of a comprehensive approach for infants presenting with an apparent life-threatening event as evidenced by prolonged infant apnea. We felt compelled to use the above comprehensive approach because detailed information regarding this problem was not readily available and practices varied substantially from center to center. Several interesting points emerged from this study. Outside the neonatal period, 1 in 300 infants had apnea as an apparent life-threatening event. Infants in group 1 belonged to a number of diagnostic categories. A detailed history, physical examination, and investigations helped to identify those problems. Once the underlying cause was identified, it became easy and clear to further manage this group.

None of the infants in this study were victims of child abuse, although this was carefully looked for.[13,14] In most cases the event was witnessed by someone other than the immediate care giver.

Theophylline is routinely used for treating apnea of prematurity. It is possible that the infants in group 3 had delayed central respiratory tract maturation.[15,16] Theophylline has been used with varying success in such infants.[12] In this study most of the infants in group 3 (40 of 44) showed polysomnographic evidence of improvement after theophylline therapy. As these infants did not present with another apparent life-threatening event, it is possible that theophylline had a beneficial effect. Previous reports indicated a 4% mortality for these events. All infants in our study did well. We fully recognize the lack of controls in this study, but our protocol did not allow such an alternative.

Ten infants were treated with a home monitor although six were monitored due to parental pressure. Intense counseling as to the benefits and limitations of home monitoring may be the reason for such a low number. The duration of home monitoring varied, with the longest being ten months and the shortest two months. We fully realize and acknowledge the fact that the problems of the sudden infant death syndrome and apparent life-threatening events are entirely separate issues, and the connections between them are difficult to establish. It is not unusual, however, to refer to surviving infants with these events as having aborted or near-miss sudden infant death syndrome.[2,10,16] It is thus important to recognize, investigate, and treat an apparent life-threatening event because the consequences may be disastrous.

It appears that a structured approach to this serious problem is the correct one. For clarity and simplicity, a flow sheet was devised (Figure 1). In special circumstances, however, both investigations and treatment must be tailored to the patient.

Infants older than the neonatal age group may have prolonged apnea. A structured approach to the problem and solution to management seems urgently needed. Fewer apneic episodes with increasing age suggest continuing maturation of the central nervous system in these infants. Physicians caring for infants should be aware of prolonged infant apnea as an apparent life-threatening event with possible morbidity and at times death in infancy. A rational approach to the problem with appropriate counseling should decrease the necessity of home apnea monitors, as the efficacy of home monitoring is still in question. Continued research is needed to identify underlying pathologic factors that may predispose infants to the sudden infant death syndrome and other sudden deaths.

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All-Terrain-Vehicle Injuries
A Sport Out of Control

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All-terrain vehicles, originally introduced as utility vehicles to be used on farms or ranches, have now gained immense popularity in the United States as a form of recreational activity. With the increasing popularity of these vehicles, along with more powerful engines, a corresponding increase in the injury and death rates has been noted. We discuss the experience in the emergency department and trauma unit of a Southwest teaching hospital, an area where these vehicles are in use year round. We suggest ways to prevent and minimize accidents to reduce the number of injuries and deaths.

(Percy EC, Duffey JP: All-terrain-vehicle injuries—A sport out of control. West J Med 1989 Mar; 150:296-299)

All-terrain vehicles (ATVs) were first introduced in the United States in 1971. They were originally marketed for use on farms or ranches as an inexpensive alternative to tractors and trucks. Their versatility and ability to get into areas normally inaccessible to larger vehicles rapidly increased their popularity. In the early 1980s, the market expanded rapidly to include a recreational use. In an affluent society with increasing leisure time at its disposal, all-terrain vehicles have rapidly become the snowmobiles of the 1960s and 1970s, and a new sport has been introduced.[1] Manufacturers have recently developed models with more powerful engines designed for racing.

The US Consumer Product Safety Commission realized the potential for injury from the recreational use of ATVs and established an investigational task force in April 1985.[2] Their reports indicate that as of September 1986 there were an estimated 2.3 million vehicles of this nature in use in this country. They also report that in 1985 there were a total of 85,900 injuries requiring treatment in hospital emergency departments and 230 deaths resulting from ATV accidents.

In Arizona, ATVs have received a great deal of public attention in the past two years. In July 1987, the Tucson Police Department employed four officers riding four-wheeled ATVs to enforce city ordinances. These regulations prohibit the use of any motor vehicle on off-road areas within a quarter mile of any inhabited structure. The stated purpose of this ordinance was to safeguard riders and minimize complaints received from residents living near popular off-road sites. More recently, additional legislation requires that vehicles purchased on or after August 7, 1985, have certificates of title and numbered license plates. Owners wishing to operate these vehicles on public roads must have a horn, a rearview mirror, eye protection, two brake systems, a muffler, head-, tail-, and stoplights, and lights on the license plates.

Apart from injuries to the driver and passenger, these vehicles can, of course, cause injuries to other drivers or pedestrians. The issues of noise pollution and damage to the environment must also be considered. With these vehicles, game can be tracked and chased down in open areas, and thus they pose a definite danger to the natural environment. Plants, bushes, and the banks of dry river or creek beds are at risk of being irreparably damaged.

Patients and Methods

Included in our study are patients who presented to the University Medical Center (UMC; Tucson) emergency department who had sustained ATV-related injuries. The study included accidents that were reported from January 1985 through July 1987. The University Medical Center is one of two large hospitals in the Tucson area that offer a full-service level I trauma center. Seven other hospitals with emergency departments serving Tucson and the surrounding communities were not included in this study. The UMC is one of three hospitals in Arizona that the Consumer Product Safety Commission (CPSC) has elected to use to monitor the number of persons seen in emergency departments with ATV-related injuries.

Using CPSC records, we identified 57 ATV-related accidents whose victims presented to the UMC Emergency Department in that time frame. Of these, 55 had medical records from which we were able to verify that the injuries were indeed ATV-related so as to carry out a retrospective study of these accidents. We determined the number of patients admitted to hospital as well as those who were treated on an outpatient basis. The related history and subsequent diagnosis and treatment of the injuries thus received were investigated in detail. The UMC Medical Information System was able to provide account records for professional services rendered in both the emergency department and in hospital and to quantitate medical costs for each patient studied.

An attempt was made to contact each of the patients in the study to obtain further information and complete the documentation in the medical records in a number of areas. Such factors as patients' level of experience in driving all-terrain

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ABBREVIATIONS USED IN TEXT

ATV = all-terrain vehicle
CPSC = US Consumer Product Safety Commission
UMC = University Medical Center

vehicles and whether they were the actual driver or the passenger; the type of vehicle involved (three or four wheeler), the use of alcohol, whether or not helmets had been worn at the time of the accident, and the type of terrain and mechanics of the injury were all investigated. Of the 55 patients whose records were available, only 28 could be contacted by telephone. All patients who were interviewed agreed to answer questions about their accidents, although they were initially hesitant. Many of the patients stressed that they were ardent ATV enthusiasts and did not wish to give the vehicle a bad name. Only after we had assured them that we were simply carrying out a medical study on the nature of the injuries rather than an adversarial attack on the equipment were they willing to discuss their case histories. They emphatically did not wish the sport to be maligned, nor did they wish to see it banned on the basis of adverse publicity. National figures for sales, injuries, and fatalities were obtained from the CPSC.[3,4]

Results

Of the 33 patients interviewed or whose charts specified, 27 (82%) were driving the vehicles when they were injured and 5 (15%) were passengers. One patient was struck by an ATV while walking. There was only one accident in which both driver and passenger were injured. Of the 55 patients whose records were studied, 7 (13%) were female, and one of these women was pregnant at the time of her accident. We do not know if the outcome of her pregnancy was affected by the accident (Table 1).

The ages of the patients whose records were researched ranged from 5 to 42 years, with both median and mean ages being 21 years. (There is no legal age requirement for ATV riders in Arizona.) Of the 55 persons, 15 (27%) were younger than 16 years and 5 (9%) were younger than 12 years. The CPSC ATV task force judged children younger than 16 to be at a greater risk for injury or death than adults. This was felt to be "due to poor judgment and failure to recognize and operate ATVs within their skill levels." The task force also concluded that children younger than 12 are unable to operate even the smaller models safely because they lack the physical size and strength, cognitive abilities, motor skills, and perception.[2]

The use of alcohol while riding was an additional risk factor for accidents. Of 27 of those patients contacted, 8 (30%) admitted to having ingested alcohol either during or just before the ride. In addition, three of the patients not contacted had blood alcohol concentrations recorded in their medical charts of 0.105, 0.183, and 0.232 mg per dl, respectively. All of these levels were in excess of the legal limit of 0.1 mg per dl. None of the other patients in the chart study group had blood alcohol levels reported in their charts.

Skill levels and experience in handling ATVs are difficult to assess. We developed three categories to describe the experience level of the study group. Those patients who had never ridden before or who had only ridden on a maximum of

TABLE 1.—*Demographics of 55 All-Terrain-Vehicle Injuries*

Vehicle involved	
3 Wheels, %	94
4 Wheels, %	6
Person injured (N=33)	
Driver, %	82
Passenger, %	15
Pedestrian, %	3
Sex	
Male, %	87
Female, %	13
Ages, years	5-42
Median, years	21
Admitted alcohol use	
No. (%)	8 of 27 (30)
Helmet use, %*	44

*100% of patients suffering head injuries with concussions were not wearing helmets.

TABLE 2.—*Injuries Sustained From All-Terrain-Vehicle-Related Accidents (n=55)**

Injuries	*Patients, Number*
Head, Neck, and Facial Injuries	
Concussions	9
Lacerations	
Scalp	5
Face	6
Subdural hematoma	2
Basilar skull fracture	2
Cerebellar and brain-stem contusion	1
Subconjunctival hematoma	1
Contusions, facial area	5
Fractured mandible	1
Fractured nasal bones	2
Broken teeth	1
Injuries to Trunk	
Ruptured spleen	1
Contusion, thorax	2
Lacerations, scrotum, and contusion, femoral artery	1
Fractured thoracic vertebrae	1
Lumbar spinal strain	2
Injuries to the Extremities	
Dislocations, joints	
Acromioclavicular	2
Glenohumeral	1
Distal radioulnar	1
Metatarsophalangeal	1
Fractures	
Clavicle	1
Radius and ulna	1
Radius	2
Scaphoid	1
Lateral femoral condyle	1
Distal femoral epiphysis	1
Tibia	3
Navicular bone	1
Metatarsal bone	1
Sprains, ligaments	
Torn posterior cruciate	1
Ankle	1
Lacerations	6
Hematoma	2
Puncture wounds (thorns)	2
Contusions	8

*Some patients had more than one type of injury.

two previous occasions were designated as inexperienced riders. Experienced riders included those who had ridden regularly for at least a year. The intermediate group is made up of those patients who had ridden on at least three occasions but who had not ridden regularly for a full year. Of 27 riders, 7 (26%) were inexperienced, 8 (30%) were intermediate as far as experience was concerned, and 12 (44%) were experienced riders.

Of the 55 persons, 19 (34%) had injuries serious enough to be admitted to hospital at the time of the accident or at a later date for elective procedures. A study was done of the emergency department, hospital, and professional fees from the UMC to determine approximate health care costs of these all-terrain-vehicle injuries. These factors do not include charges for follow-up care outside the UMC or from other physicians to whom patients may have transferred. Thus, these figures would obviously underestimate the total costs involved in treating some of these injuries. The patients who were admitted had a mean hospital stay of 5.2 days with mean charges totaling $7,247.02. Nearly two thirds of patients (36) were not admitted and had mean charges of $568.52 for their emergency department care and follow-up clinic visits.

Perhaps the most significant statistics we gathered were those comparing the types of ATVs involved in the accidents. Three-wheeled ATVs were almost exclusively responsible for the accidents in this study, 30 of the 32 (94%) patients for whom this information was available having been riding this type of vehicle when injured.

The injuries sustained by these patients were diverse, and many had more than one injury (Table 2). Most of the injuries involved the extremities and included fractures, dislocations, hematomas, puncture wounds, contusions, lacerations, and sprains.

Of the 55 charts reviewed, only 36 mentioned whether or not a helmet had been worn at the time of the accident. Of this group, 20 (56%) were not wearing helmets. There was a significant number of head injuries, nine of which resulted in temporary loss of consciousness, and none of these nine riders were wearing helmets at the time of their accidents. Two of this group had basilar skull fractures and subdural hematomas. One was 31 years old and continues to suffer a mild deficit of recent memory. The other was a 12-year-old who required craniotomy, partial temporal lobectomy, and ventriculostomy. His disabilities of slow mental processes, confusion, and poor word selection have persisted. Another patient in this group was diagnosed as having cerebellar and brain-stem contusion. At the time of discharge five days after the accident, he continued to have difficulty with recent memory. Other head injuries included scalp and facial lacerations, subconjunctival hemorrhage, mandibular fracture, nasal bone fractures, and a patient with broken teeth and a maxillary fracture (requiring surgical reconstruction). Of the 21 patients with head injuries, 12 were not wearing helmets, while 6 were helmeted. It was not known whether the remaining three in this group were using protective headgear. Among the six wearers, the trauma was minor and included scalp and facial lacerations and nasal injuries.

Injuries to areas other than the head or extremities included clavicle fractures, thoracic vertebral compression fractures, back muscle strains, a mild splenic rupture (not requiring surgical repair), and a groin injury. The groin injury was severe with lacerations of the scrotum and extravasation of one testicle. In addition, the patient sustained an intimal dissection and thrombosis of the right femoral artery requiring a vein graft.

During the period in which our study was carried out, there were eight deaths reported in Arizona that were directly attributable to ATV accidents.[4] Two drivers hit trees and one struck a telephone pole, while two ran into road vehicles. Two ATVs overturned, killing the drivers, and the cause of one other death was unknown.

Discussion

Most of the accidents and injuries presented in this study could have been avoided or prevented. The obvious preventive measures that are available include the use of protective gear such as a helmet, goggles, heavy clothing, gloves, and appropriate footwear. None of our patients with head injuries involving loss of consciousness were wearing helmets. Abrasions and lacerations to the extremities can be prevented or minimized by wearing long-sleeved shirts and heavy pants. Riders wearing boots can decrease trauma to the feet and ankles. The patient in our study group who lost two toes was riding barefoot. Because driving an ATV requires an alert and coordinated rider, combining drinking and driving makes little sense. Unfortunately, it is not illegal, and 30% of our study group contacted by phone admitted to drinking at the time of their accident.

Indirect injuries can, of course, result from this form of recreational activity. For example, in this particular area of the Southwest, running out of gasoline or having a mechanical breakdown while in the desert might involve walking long distances back to the point of departure. This could result in severe dehydration and even death for the unprepared driver or passenger. These vehicles are also used in the northern part of the state in heavy snow, which could lead to hypothermia-related problems.

There are modifications that can be made to the vehicles themselves. The most important of these has been the change from three-wheeled vehicles to the four-wheeled models. As Figure 1 shows, the righting moment of an object is equal to the force required to overturn that object in a direction perpendicular to one side of its base.[5] This force is directly proportional to the distance from the center of gravity to the base. In an all-terrain vehicle, the base is represented by lines connecting the tires. The height of the center of gravity is also a variable in this equation. These vehicles have relatively high centers of gravity. Practically speaking, this means that three-wheeled ATVs are more apt to overturn while making turns or traveling on a grade. Four-wheeled ATVs are more stable than three-wheeled versions, but their high center of gravity still makes them prone to overturning. Though many of the injuries in our study were not sustained in roll-over accidents, three-wheeled ATVs were involved in 94% of all accidents. All-terrain-vehicle manufacturers and local retailers were reluctant to share sales data that would give us an accurate ratio of three wheelers to four wheelers in use, thus defining the significance of the 94% figure. The CPSC reported in their analysis of injuries and deaths that the relative risk of injury on four wheelers is 65% of the risk on three wheelers.[3] Interestingly enough, the risk of death is the same for the two models. As of January 1988, ATV manufacturers have agreed to stop producing the three-wheeled vehicle. A large number of the three wheelers has been pro-

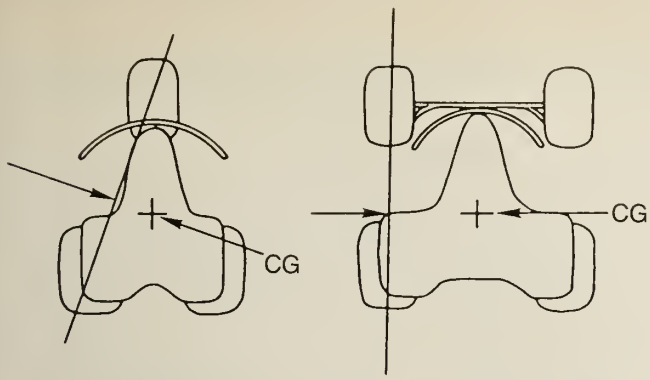

Figure 1.—The righting moment of four-wheeled all-terrain vehicles is greater than that of three-wheeled vehicles, giving greater stability, especially in turning (from Stevens et al[5]). CG = center of gravity

duced to date, however, and will continue to be in use for many more years, thus perpetuating an increased risk to riders and passengers.

Several other modifications to improve safety have been proposed. Superficially, the use of seat belts seems to be a good idea. In the event of overturning, however, the argument can be made that restraining the riders may subject them to trauma from the rolling vehicle. The CPSC report on deaths involving ATVs reveals that while indeed many riders were thrown from their vehicles, the scenario of the vehicle landing on the rider occurred in 26% of all deaths. These data are a contraindication to the use of seat belts unless the additional modification of a roll bar is adopted. A sturdy metal leg guard could prevent injuries sustained when the vehicle sideswipes rocks, stumps, and brush. A leg guard would also reduce crush injuries produced when the leg becomes pinned against an object or the ground.

Even with proper clothing and equipment, drivers are ultimately responsible for the safety of themselves and others who may cross their paths. There are no laws in Arizona governing speed or the use of alcohol while driving ATVs. Those laws that restrict the use of ATVs to preexisting trails and prohibit their use in some areas are difficult if not impossible to enforce. The use of these vehicles on paved roads is illegal, and this law should be strictly enforced. (One of our patients was severely injured in a collision with a truck.) There is no minimum age requirement for operating an ATV in Arizona, and 27% of our study group were younger than 16 years. According to the CPSC, the smaller ATV models targeted at this age group offer no decrease in the risk of injury.[2] It appears that judgment is the key variable in the higher risks for riders aged 12 to 16. The CPSC also found that high speeds correlated well with fatalities, though not as well with injuries.[3] Some ATV manufacturers have added two well-thought-out features to their newer models. One is a throttle governor, a device that allows the throttle to be locked at a desired maximum. The other device is a remote control that allows the vehicle's motor to be shut off if a child riding the vehicle displays unsafe speed or maneuvers. Obviously, both of these features require parental or other adult supervision to be successful.

On another positive note, as the sport grows in popularity and numbers, several organizations have formed to promote safety and environmental conservation. The Specialty Vehicle Institute of America was formed in 1983 by ATV manufacturers to provide safety information and instructions to ATV riders nationwide. The United Four Wheel Drive Association is made up of state chapters of off-road enthusiasts who are active in maintaining the environment (R.G. Stahl, "Off-Road Vehicles: A Disquieting Look at a Major Environmental Threat," *Arizona Highways,* August 1987, pp 5 to 13). The Arizona state chapter is involved in rehabilitating fragile desert areas damaged by these vehicles and helps the US Forest Service patrol areas most susceptible to damage from irresponsible off-road driving. Many feel that more severe penalties and designated trails are necessary to limit the widespread environmental damage already occurring over much of Arizona's wilderness.

Conclusions

All-terrain vehicles allow travel over lands previously reachable only on foot or by horseback. The three and four wheels give riders a false sense of stability compared with two-wheeled cycles, and thus less experienced drivers feel comfortable on rough terrain or at high speeds. Traveling across country subjects riders to unforeseen changes in land contour, and for this reason preexisting trails are much safer.

We are hopeful that legislation and instruction will catch up with the sport as it grows. Current regulations and monitoring, whether governmental or internal, are inadequate as evidenced by the high injury and death rates, as well as the already significant environmental impact by ATVs. Wearing proper clothing and modifying the ATVs themselves will decrease injuries. The most significant of these measures appear to be the use of a helmet and the increased stability of four-wheeled models. Ultimately, the safety of any motor vehicle depends on the sound judgment of its operator. With the continued efforts of safety- and environment-conscious riders and an industry that is also responsive to these issues, ATVs can reach their full potential as recreational vehicles.

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Clinical Medicine

A Seroepidemiologic Survey of Human T-Cell Lymphotropic Virus Type I in Two Hawaiian Hematologic-Oncologic Practices

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A seroepidemiologic survey for antibodies to the human T-cell lymphotropic virus type I (HTLV-I) was carried out in two Hawaiian hematologic-oncologic practices. Specimens of serum or plasma from 215 donors were assayed using the ELISA technique, followed by the Western blot technique to confirm antibody specificity to HTLV-I. Of 214 seropositive donors, 16 (7.5%) were positive. Of 172 donors of Japanese ancestry, 16 (9.3%) were seropositive; none were white, Chinese, Filipino, or Pacific Islander. One donor contracted the virus through blood transfusions. The results suggest that HTLV-I was introduced to Hawaii with the Japanese immigration.

(Kimata JT, Kaneshiro SA, Kwock DW, et al: A seroepidemiologic survey of human T-cell lymphotropic virus type I in two Hawaiian hematologic-oncologic practices. West J Med 1989 Mar; 150:300-302)

The human T-cell lymphotropic virus type I (HTLV-I), an exogenous type C retrovirus, was first isolated and identified from a patient in the United States with cutaneous T-cell lymphoma.[1] Since that time, HTLV-I has been found to be endemic in various parts of the world—southwestern Japan, the Caribbean islands, South America, southeastern United States, and Africa; it has also been detected in southern Italy, Israel, and the Arctic region.[2-9]

Studies done to find a relationship between HTLV-I infections and malignant tumors show the virus is associated with adult T-cell leukemia or lymphoma (ATL).[10,11] On the other hand, no relationship exists between the virus and cutaneous T-cell lymphoma, as originally thought. HTLV-I apparently occurs with equal frequency in men and women. Interestingly, the number of persons HTLV-I-positive in a population increases significantly with age, and the incidence of HTLV-I among relatives of HTLV-I-positive persons is higher than the incidence in a general population.[12-14]

Several modes of transmission exist: mother to child after birth, sexual, and blood transfusions.[12,14-16] Hino and co-workers and Robert-Guroff and associates suggest that mother-to-child and husband-to-wife transmissions are responsible for the higher incidence of HTLV-I infection among relatives than in a general population.[12,14] One implicated mode is breast-feeding; specimens of milk from seropositive mothers have contained HTLV-I-positive lymphocytes.[12] Sexual contact is responsible for marital transmission.

Okochi and colleagues have shown that blood transfusions are a second pathway for HTLV-I infection.[17] Recipients of one to two units of whole blood from HTLV-I-positive donors showed gradually rising titers of antibodies to HTLV-I after a transfusion. HTLV-I-positive cells were detected in the recipients' cultivated cells.

The spread of HTLV-I infection by insect vectors has been hypothesized but not proved.[3,15] This possibility has not been excluded since it is still questionable whether the other two routes—familial contact and blood transfusions—can account for such high HTLV-I prevalence in areas such as southwest Japan.

The origin of HTLV-I is thought to be Africa. Wong-Staal and Gallo hypothesized that the virus originated in Africa and spread to other endemic regions through commercial and slave trading, which dates back to the 16th century.[2] Furthermore, Robert-Guroff and co-workers and Tajima and associates suggest that immigration and tourism continue to spread HTLV-I to nonendemic areas.[9,18] This type of introduction along with sexual transmission may explain why the virus occurs in clusters. A similar situation may have occurred in Hawaii.

Nakamura and colleagues reported the first group of patients with ATL in the Japanese population of Hawaii in 1984[19]; all were positive for the HTLV-I antibody. Because all the patients were of Japanese ancestry, though born in Hawaii, it is likely that HTLV-I has been introduced to Hawaii with this population.

To assess the prevalence of HTLV-I, we initiated a seroepidemiologic study in two Hawaiian hematologic and oncologic practices.

Subjects and Methods

Specimens of serum or plasma were drawn from 215 subjects (104 men and 111 women) between March 1984 and August 1986. The subjects' ages ranged from 19 to 96. They

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ABBREVIATIONS USED IN TEXT

ATL = adult T-cell leukemia or lymphoma
ELISA = enzyme-linked immunosorbent assay
HTLV-I = human T-cell lymphotropic virus type I

were mainly patients of two Hawaii hematologists-oncologists in private practice. In all, 2 patients had ATL, 15 had other leukemias or lymphomas, 54 were diagnosed with other malignant diseases, and 143 were either healthy or patients with nonmalignant diseases. All specimens were stored at −20°C (−28.9°F).

Two assays were used in this study: the enzyme-linked immunosorbent assay (ELISA) and the Western blot technique. The Western blot assay was used to confirm the ELISA results. Both methods have been described in depth in the *Hawaii Medical Journal.*[20]

Results

A total of 215 donors were tested for antibodies to HTLV-I. Of these, 14 (6.5%) were seropositive by the ELISA assay and 16 (7.5%) by Western blot. Using the Western blot technique, we detected only one false-positive. Table 1 gives the percentage of subjects who were seropositive by ethnicity. Of the 172 donors who were of Japanese or Okinawan ancestry, 16 (9.3%) were seropositive compared with 0 of 43 non-Japanese/Okinawan subjects. This was a significant difference (Fisher's exact test, single-sided, $P = .03$).

As in previous seroepidemiologic studies on HTLV-I, the mean age of the seropositive donors was high: 66.2 years (the age range was 35 to 95 years). More women than men were positive, however: 13 versus 3, respectively (Table 2).

TABLE 1.—*Incidence of Seropositive Donors by Ethnic Background*

Ethnic Background	*Number Positive/Total (Percent)*
Japanese/Okinawan	16/172 (9.3)
White	0/18 (0.0)
Chinese	0/15 (0.0)
Filipino or Pacific Islander	0/9 (0.0)

Table 2 shows the place of birth for the seropositive persons. The towns or cities where the Hawaii-born subjects (12) were born and the first generation settled were Honolulu, Hilo, Lahaina, Kohala (Kapaau), and Kapakolua. Patient 9, who was a Japanese immigrant and had several transfusions between June 1985 and June 1986, apparently was seronegative in June 1985 but positive in June 1986. Patients 1 and 2 were the only family members tested; they were mother and daughter, respectively.

Finally, Table 2 lists the diagnoses of the HTLV-I-positive donors. All subjects diagnosed with ATL (2) and tropical spastic paraparesis (2) were positive. Three of five patients diagnosed with acute nonlymphocytic leukemia were positive, and two of five patients with eosinophilia were positive. None of the patients diagnosed with other leukemias or lymphomas were positive. Of 12 patients with colon cancer, 1 was positive. Only 1 of 66 normal and 5 of 70 donors diagnosed with other nonmalignant diseases were positive.

Discussion

Nationwide seroepidemiologic studies in Japan have shown that the southwest area of the country is a region endemic for HTLV-I.[11] Results from preliminary studies suggest that HTLV-I was introduced to Hawaii by the early Japanese immigrants. Many who left Japan for Hawaii to work on sugar plantations came from places such as Wakayama, Fukuoka, Okinawa, and Hiroshima.[21] These prefectures are identified as endemic for HTLV-I (Wakayama, 13%; Fukuoka, 17%; Okinawa, 10%; Hiroshima, 3%).[11]

The virus has a low infectivity; transmission results in the event of close contact or the actual transmission of infected cells. Hence, a familial environment is usually necessary. We have confirmed one case of mother-to-child transmission of the virus (Table 2, patients 1 and 2). The origin of HTLV-I for the other Hawaii-born seropositive donors is more difficult to analyze because several years have passed since their parents died. Because HTLV-I has a low infectivity, it is most probable that these seropositive donors received exposure from their parents. On the other hand, we cannot rule out parasitic infestations or sexual contact. Family members (maternal and paternal) are currently being tested.

As mentioned, only donors of Japanese ancestry are sero-

TABLE 2.—*Demographics and Diagnoses of Patients Seropositive for HTLV-I*

Patient	*Age, years*	*Sex*	*Assay*		*Birthplace*	*Diagnosis*
			ELISA	*Western Blot*		
1	35	♀	+	+	Hawaii	Normal
2	..	♀	+	+	Hawaii	Adult T-cell leukemia/lymphoma
3	60	♀	+	+	Hawaii	Rheumatoid arthritis and interstitial fibrosis
4	84	♀	+	+	Okinawa	Osteoarthritis, degenerative disc disease, anemia, hypertension
5	63	♀	+	+	Hawaii	Evolving adult T-cell leukemia/lymphoma
6	40	♂	+	+	Hawaii	Acute nonlymphocytic leukemia
7	88	♀	+	+	Okinawa	Idiopathic thrombocytopenic purpura
8	57	♂	+	+	Hawaii	Thrombotic thrombocytopenic purpura
9	56	♀	+	+	Honshu, Japan	Acute nonlymphocytic leukemia
10	66	♀	−	+	Hawaii	Thrombocytosis
11	70	♀	−	+	Hawaii	Not available
12	96	♀	+	+	Okinawa	Chronic rash, eosinophilia, hepatitis B
13	69	♂	+	+	Hawaii	Colon cancer, non-A, non-B hepatitis
14	79	♀	+	+	Hawaii	Mild eosinophilia, diabetes mellitus, hypertension
15	59	♀	+	+	Hawaii	Tropical spastic paraparesis
16	71	♀	+	+	Hawaii	Tropical spastic paraparesis

HTLV-I = human T-cell lymphotropic virus type I, + = positive, − = negative

positive. Among first- and second-generation immigrants, few intermarriages took place. In succeeding generations, HTLV-I may spread to other ethnic groups as acculturation occurs.

Of the 16 seropositive donors, 1 (patient 9) received exposure through blood transfusions. This person had several transfusions between June 1985 and June 1986 and became seropositive in that time period. Details have been reported elsewhere.[20] Because Hawaii may have a high incidence of HTLV-I carriers in the Japanese population, it may be of significant importance to screen possible blood donors of this ethnic group for antibodies to HTLV-I to prevent infection by transfusion.

Until recently, adult T-cell leukemia or lymphoma had been the only disease associated with HTLV-I infection.[22] Here we report that both patients in our survey who have ATL are antibody-positive to HTLV-I. Tropical spastic paraparesis, a slow, progressive myelopathy, also appears to be associated with HTLV-I infection.[23,24] Antibodies to HTLV-I and viral antigens have been detected in the serum and cerebrospinal fluid, and proviral sequences have been detected in fresh peripheral blood mononuclear cells and cell cultures of spinal fluid of patients with tropical spastic paraparesis. The virus is found in T-cell lines derived from the peripheral blood and cerebrospinal fluid of these patients. Both patients with tropical spastic paraparesis in this study are antibody-positive. No conclusion can be drawn about the relationship between the diagnoses of the other patients and HTLV-I positivity at this time.

Although the patient sample is small and predominantly of Japanese and Okinawan origin, we still believe that HTLV-I has been introduced to Hawaii with the Japanese and Okinawans. There are several reasons. First, immigrant Japanese workers came from HTLV-I-endemic regions of Japan. Second, four seropositive patients are from Japan or Okinawa, and two Hawaii-born subjects, cases 15 and 16 (Table 2), who indicated their family origin, have parents from Okinawa and Wakayama, Japan, respectively. Third, non-Japanese families did not originate from identified HTLV-I-endemic regions. Further testing will help to further confirm this hypothesis.

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Clinical Review

Strategies in Managing Asthma

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The management of adult asthma involves a concerted effort to identify and remove or mollify inciting or triggering stimuli such as respiratory tract infections, gastric reflux, aspirin, β-antagonists, and environmental agents; educate patients, using written treatment plans and pulmonary function monitoring; and properly use the antiasthmatic medications including β-agonists, theophylline, anticholinergics, and corticosteroids, with an emphasis on aerosol delivery and the use of corticosteroids during exacerbations. This strategy is summarized with suggestions on therapy in emergency departments, during the transition from hospital to ambulatory care, before exercise, and during pregnancy.

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A reexamination of the management of asthma is worthwhile for several reasons:

- Asthma is frequently encountered in medical and surgical practices. The prevalence of asthma in the adult population is about 3% to 5%, whereas wheezing or cough associated with episodes of respiratory tract infections or exposure to noxious fumes is probably four or five times more frequent.[1]
- More effective and specific antiasthmatic medications and a wider variety of dosing and delivery strategies are available than were ten years ago.
- Clinical studies and experiments in animals raise concern about arrhythmogenesis with some of these medications, and epidemiologic studies from New Zealand and the United States suggest a small but definite increase in mortality from asthma, with nearly all studies implicating undertreatment rather than overtreatment.[2]

In this review I will focus on managing adult asthma in clinical practice. The discussion of therapy will be limited to the major antiasthmatic medications.

Asthma still eludes a precise definition, although airway hyperresponsiveness, epithelial damage, luminal- and mural-activated inflammatory cells including eosinophils and their breakdown products, and impaired mucociliary clearance are thought to play major roles in its genesis and perpetuation. All these factors lead to a decrease in the cross-sectional area of airways and the physiologic hallmarks, decreased but (partly) reversible expiratory flow, increased airway resistance, and increased airway reactivity to a variety of stimuli.

Assessing Severity of an Asthma Attack

In patients with asthma, auscultatory expiratory wheezing is a helpful physical sign, but its absence may be indicative of advanced disease or severe decompensation. The use of accessory muscles of respiration (trapezius, sternocleidomastoid), an abnormal phase lag of rib cage and abdominal motion,[3] and a paradoxic pulse pressure correlate with the severity of an attack. Scoring systems based on the results of a physical examination in the emergency department to assess the need for admission to hospital are probably more useful in sharpening diagnostic skills than in making absolute decisions about the need for hospital care.[4-6] Spirometric testing including measurements of the forced vital capacity, the forced expiratory volume in one second (FEV_1), and the ratio of the FEV_1 to the forced vital capacity can confirm an initial diagnostic impression, be used to follow a patient, and help decide the need for admission to hospital and a new medication or an increased frequency of dosing. Home diaries and monitoring of pulmonary function with spirometry or peak flow meters are particularly useful aids in patients with difficult-to-control asthma to provide evidence of deterioration.

Systems that grade an asthma attack by arterial blood gas measurements may be no better than spirometric measurements, but determining the arterial blood gases plays a crucial role in assessing the severity of decompensation of any patient with acute breathlessness including asthma. A rising or "normal" partial carbon dioxide pressure and declining pH are indicators of ventilatory insufficiency requiring close observation and aggressive management. Although clinicians often take chest radiographs on patients with possible asthma, their diagnostic usefulness for asthma is low. They are most useful to help sort out other confounding diseases (pneumonia, pulmonary edema, tumor, pneumothorax) in an acutely breathless patient.

In patients with possible asthma, microscopic examination with a Wright's or Giemsa stain of a deep expectorated sputum specimen for eosinophils, clumps of desquamated epithelial cells, Charcot-Leyden crystals (granular debris from eosinophils), and Curschmann's spirals (concretions of glycoprotein, eosinophils, and Charcot-Leyden crystals) provides evidence of airway obstruction. Charcot-Leyden

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in 1 second
MDI = metered-dose inhaler

crystals may be found in patients with respiratory tract infections and asthma whereas major basic protein in sputum may be more specific for asthma.[7]

Therapy

Once the diagnosis of asthma is confirmed or strongly suspected, a first step in management is an explanatory session with the patient about triggering factors to avoid (Table 1), the proper use and side effects of medications, early and alarming symptoms to expect with exacerbations, the use of a symptom diary or home pulmonary function monitor (or both), and written treatment plans. The goals of therapy must be clear in the minds of both the patient and clinician—that is, reduce the number and severity of attacks, maintain functional status, and maintain maximal bronchodilation. Patient-oriented literature should be provided to allow for personal review, insights, and expectations. The following discussion highlights the major antiasthmatic drugs. The use of inhaled agents has gained credibility over the oral agents, and they are preferred.[8]

TABLE 1.—*Stimuli That Trigger or Incite Asthma*

- Respiratory tract infection
- Medications or additives
  - β-Antagonists—oral, parenteral, or ophthalmic
  - Aspirin
  - Nonsteroidal anti-inflammatory agents
  - Sulfites and other preservatives
- Allergens
- Gastroesophageal reflux
- Certain work and home environments
- Exercise and hyperventilation

TABLE 2.—*Technique for Using a Metered-Dose Inhaler*

- Shake the inhaler
- Place mouthpiece 2 cm from lips; aim towards throat
- Relax and exhale
- Actuate the inhaler, followed by complete inhalation over 3 to 5 seconds
- Hold breath for 10 to 20 seconds
- Relax and exhale
- Repeat second puff 2 to 4 minutes later

Medications

β-Agonists

The β-adrenergic agonists are potent, convenient, efficient, and economical first-line agents for the treatment of asthma. Their action is primarily to relax bronchial smooth muscle, but the inhibition of bronchoconstrictive mediators, augmentation of the fatigued diaphragm, and improved mucociliary transport may contribute to their effectiveness. The noncatechol β_2-selective agonists have become powerful agents for management strategies. These agents are not metabolized by catechol-O-methyl transferase and monamine oxidase and have extended half-lives. They are also resistant to the gastric and intestinal sulfakinases so that oral delivery is feasible.

The β_2-agonists are versatile and can be delivered by aerosol, oral, and intramuscular routes. Inhaled β_2-agonists act within 5 to 10 minutes with peak effect at 45 to 90 minutes and a duration of 3 to 6 hours depending on the agent and efficiency of delivery. For patients who can use a metered-dose inhaler (MDI) properly, this aerosol is the preferred method of administration. The importance of a trained person instructing in the proper technique needs emphasis (Table 2). A hand-held bulb or powered nebulizer may deliver more medication and is an alternative. The expense, cleaning, time for aerosol delivery, and lack of portability of powered nebulizers are drawbacks.[9] Delivery by an intermittent positive pressure breathing device offers no advantages over the other delivery routes. Spacers and reservoirs that attach to an MDI have the advantages of allowing a longer time period for delivery to patients and reducing oropharyngeal deposition. Enhanced bronchodilation has been difficult to prove with these devices, but their use is recommended in patients who have trouble coordinating the actuation of an

TABLE 3.—*β-Agonist Formulations, Properties, and Dosing*

Property or Dosing	*Isoproterenol*	*Bitolterol Mesylate*	*Isoetharine*	*Metaproterenol Sulfate*	*Terbutaline Sulfate*	*Albuterol*
Onset of action (aerosol), min	5	10	10	10	10	10
Peak, min	15	60	30	45	60	60
Duration, h	1	3-8	2-3	3-6	4-6	4-6
MDI dose/puff, mg	0.16	0.37	0.34	0.65	0.20	0.09
Frequency, No. of puffs	Not useful	2 q 4-8 h	2 q 3-4 h	2 q 4-6 h	2 q 4-8 h	2 q 4-8 h
Oral dose, mg	NA	NA	NA	10, 20	2.5, 5	2, 4; 4 extended release
Frequency, mg	NA	NA	NA	10 q.i.d. or t.i.d.	2.5 t.i.d.	2 t.i.d.; 4 b.i.d., extended release
Intramuscular dose, ml	NA	NA	NA	NA	0.25	NA
Cost/d, $						
Aerosol	..	0.50	0.52	0.43	0.50	0.47
Oral	..	..	..	0.45	0.55	0.60 0.70 (extended release)
Side effects						
Aerosol	Tachycardia	Tremor, tachycardia	Rare tachycardia	Rare tachycardia	Rare tachycardia	Rare tachycardia
Oral	NA	NA	NA	Tremor, tachycardia	Tremor, tachycardia	Tremor, tachycardia

b.i.d. = twice a day, MDI = metered-dose inhaler, NA = not available, q = every, q.i.d. = 4 times a day, t.i.d. = 3 times a day

MDI.[10] The convenience of a tablet is appealing, but equal bronchodilation and fewer side effects occur with aerosol systems. Intravenous β_2-agonists have been advocated for some patients with severe refractory asthma,[11] but others have shown no advantage over the aerosol route.[12]

Table 3 compares the β-agonists available in the United States. Although isoproterenol and isoetharine are still available, their use is rarely indicated with the advent of safer, longer-acting, and equipotent β_2-agonists. Metaproterenol sulfate and terbutaline sulfate were first introduced in the United States in the mid-1970s followed five years later by albuterol. All three have had extensive and favorable evaluation and scrutiny. Bitolterol mesylate, a recently released, sympathomimetic amine aerosol, undergoes hydrolysis after delivery, releasing the active catecholamine, colterol. In limited studies bitolterol showed similar efficacy, duration of action, and safety when compared with albuterol.[13] Fears about abuse and delayed contact with physicians at times of asthma exacerbations prevented the over-the-counter release of metaproterenol in an aerosol in 1983.[14] Although aerosol epinephrine has been widely available over the counter, its efficacy has not been compared with that of prescribed agents in a rigorous study.

Side effects of the β-agonists include musculoskeletal tremor and tachyarrhythmias, although these are uncommon with aerosol delivery as compared with the oral route. Hypokalemia and hyperglycemia occur in some patients.[15]

Theophylline

Anhydrous theophylline enjoys widespread acceptance and use in the United States but is relegated to a secondary or tertiary role in Great Britain and parts of Europe. The primary action of theophylline remains as a bronchial smooth muscle relaxant, but several other potentially beneficial properties have been found, including respiratory center stimulation, augmentation of the hypoxic ventilatory response, improved mucociliary clearance, improved diaphragmatic contractility, inotropic right ventricular performance, and mild diuresis.[16]

Major advances have been the development of sustained-release formulations (8- to 12-hour duration)[17] and the availability of serum concentration measurements to help titrate dosing. Theophylline in a 24-hour sustained-release form is available, although nocturnal or early morning breakthrough and dumping with high-fat meals are still problems in some patients. Administering such preparations at bedtime may circumvent those problems.[18] Some patients—young children, stroke victims, or others with impaired swallowing—are unable to ingest theophylline tablets. Alternative strategies include the oral or feeding tube administration of theophylline (nonalcoholic) liquid or the beads from a capsule or "sprinkle" preparation. Aminophylline—the ethylenediamine salt of theophylline—remains the only soluble theophylline for intravenous administration. Aminophylline rectal suppositories should no longer be used in adults because of erratic absorption and mucosal irritation.

Theophylline treatment of asthmatic patients in hospital requires the rapid availability of serum concentrations. Although acutely ill patients show an increasing bronchodilating effect of theophylline with serum levels above 20 μg per ml, individual patient titration is needed to avoid toxic effects. Optimal theophylline serum concentrations are between 10 and 20 μg per ml. There are few, if any, indications for pushing the theophylline level to above 20 μg per ml. With oral theophylline preparations in the outpatient setting, the role and frequency of determining serum levels are less clear. If patient complaints or findings suggest toxic side effects, a serum level in the high teens or above 20 would provide useful confirmation. If there is a question about the adequacy of therapy or patient compliance, a serum measurement to show low levels (<8 to 10 μg per ml) is useful. With the introduction of reliable and less expensive office kits, a greater use of the outpatient determination of theophylline capillary blood levels may be indicated.[19]

TABLE 4.—*Conditions or Medications That May Require Altering Theophylline Dosage*

Need to Increase Dose	*Need to Decrease Dose*
Cigarette smoking	Liver disease
Barbiturate	Congestive heart failure
Phenytoin	Smoking cessation
	Cimetidine
	Erythromycin

Because theophylline is metabolized by the liver, any condition or drug that affects liver function may alter theophylline blood concentrations (Table 4). Distressing side effects of theophylline use include dyspepsia, nausea, and headache. Seizures and cardiac arrhythmias can be lethal but are almost always avoidable by maintaining therapeutic blood levels. Neuropsychologic and learning disorders and behavior problems have been a concern in children[20] and some adults[21] on long-term theophylline therapy, but they are difficult to prove.

With the current popularity of theophylline and β-agonist agents, concerns about cardiac side effects including serious or fatal arrhythmias have come from cardiac monitoring studies in animals and humans. High doses of β-agonists (terbutaline) and theophylline can cause subendocardial necrosis in various animal species.[22] Although the doses in animals were much higher than clinically used in humans, long-term therapy for asthma might produce comparable side effects. These lesions have been seen in a few patients dying of status asthmaticus.[23] Monitoring studies of heart rate and rhythm of patients with asthma and obstructive lung disease have shown increased and more complex arrhythmias with oral or subcutaneous β-agonist-theophylline regimens. A study in younger asthmatic patients showed an increased heart rate and complexity of extrasystoles on β-agonist or theophylline therapy alone and in combination.[24] A few clinical reports have shown deleterious effects on left ventricular function in patients on β-agonist aerosol therapy alone or in combination with theophylline.[25] The Food and Drug Administration has issued a warning about the combined drug regimen, and prudence would dictate lower dose oral combinations or aerosol agents (β-agonist, steroids) in the elderly and patients with underlying arrhythmias or coronary artery disease.[26]

Corticosteroids

More ritual and mysticism surround the use of corticosteroids in patients with asthma than any other aspect of therapy. The actions of steroids include reducing the number of inflammatory cells (including eosinophils) and the amount of mucosal edema, partial stimulation or enhancement of adenyl cyclase enzymes, potentiating the effect of or pre-

venting tachyphylaxis of other bronchodilators, blocking the release of some mediators, and diminishing airway hyperresponsiveness.[27] It remains unknown whether steroids reduce long-term sequelae, stabilize airway function, or change the natural history of the disease.

During episodes of asthmatic decompensation, steroids may be the most potent agent, and an early institution of a steroid regimen may produce dramatic relief of symptoms and findings with a single dose. Using steroids in an acutely ill person with asthma averts respiratory failure, shortens the duration of exacerbation, improves pulmonary function, ameliorates hypoxemia, and decreases the relapse rate after emergency department discharge.[28,29] Improvement in an acutely decompensated patient begins at five to seven hours, although recent studies suggest an earlier onset.[28] Most steroid preparations are relatively long-acting with biologic durations of 24 to 36 hours. The dose, frequency of administration, and preferred preparation remain controversial. The medium-dose supporters maintain that 400 to 800 mg of hydrocortisone or 80 mg of prednisone daily will be effective and has reduced side effects and cost.[30] The high-dose methylprednisolone (500 to 600 mg a day in four divided doses) advocates argue for a faster recovery, enhancement of the effects of other bronchodilators in some refractory patients, and minimal concern about side effects during a short course.[31] Several management techniques have been useful to reduce or keep steroid side effects to a minimum. The steroid dose can be rapidly reduced—three to seven days—in a patient who has never received steroids if clinical and pulmonary function is maintained. Longer tapering may be necessary if the clinical improvement is slow or long-term administration has been used in the past weeks or months. Alternate-day steroid administration is standard practice in many steroid-responsive diseases. In asthma this strategy may not be as well tolerated due to exacerbations on the "off day" unless a small dose is given.

Aerosolized steroids have been a major advance to assist asthmatic patients who require ongoing steroid therapy or who have unavoidable side effects with β-agonists or theophylline.[32] Three poorly absorbed steroid MDI preparations are available—beclomethasone, triamcinolone acetonide, flunisolide. An arbitrary starting dose is two puffs four times a day, but higher and less frequently administered doses are well tolerated. Preceding the steroid administration by several minutes with an aerosol β-agonist is thought to allow the steroid to reach smaller airways and thus improve its efficacy. Primary aerosol steroid use may be efficacious for patients with difficult tachyarrhythmias or seasonal asthma. During the transition from parenteral to aerosol steroids or other bronchodilators, nasal steroid aerosols or solutions should be used in patients with rhinitis or nasal polyposis to prevent flare-ups. Parenteral steroids are needed during an episode of asthmatic decompensation, other acute illness, or during perioperative illness.

Hoarseness, sore throat, or oral thrush will develop in about 5% of patients using steroids (oral or inhaled) long term. These side effects can be reduced by rinsing the mouth after steroid aerosol delivery, reducing the dose, or using a spacer. Postinhalation coughing, wheezing, or reductions in the FEV_1 may be a problem with beclomethasone therapy and can be eliminated by using triamcinolone.[33] All parenteral steroid preparations have variable adrenal-suppressing, ulcerogenic, salt-retaining, and gluconeogenic side effects. Because osteoporosis with an increased prevalence of rib and vertebral fractures seems to be a frequent side effect with long-term (longer than six months) steroid use, most such patients should have calcium and vitamin D supplementation, provided that they do not have hypercalciuria or other contraindications.[34]

Anticholinergic Agents

With clarification of the pathophysiologic role of the parasympathetic nervous system, improved aerosol dosing strategies, and the development of synthetic atropine derivatives, there has been renewed enthusiasm for anticholinergic therapy in obstructive lung diseases.[35] Although sometimes effective in asthma, anticholinergics may have their greatest role in chronic obstructive pulmonary disease. The peak effect of aerosol anticholinergics occurs at one hour and lasts four to six hours. Rebuck and co-workers showed that administering a combined β-agonist-anticholinergic aerosol in an emergency department may enhance bronchodilation and extend the duration of action (longer than the use of either agent alone),[36] although Karpel and associates showed no benefit (but increased side effects) with the addition of atropine sulfate to a metaproterenol regimen.[37] The quaternary ammonium derivative of atropine, ipratroprium bromide, has been recently released in the United States in an MDI. Ipratroprium is poorly absorbed from the gastrointestinal and respiratory tracts and does not cross the blood-brain barrier. Ipratroprium will supplant the use of atropine in most patients. Dose-related side effects such as gastric or urinary atony, blurred vision, desiccation of secretions, or an altered sensorium may be a problem with atropine therapy but are much reduced with the use of ipratroprium.

Cromolyn Sodium

Cromolyn is effective as a preventive medication in some patients with asthma.[38] Cromolyn does inhibit mast cell degranulation and subsequent mediator release, but its effectiveness for exercise-induced asthma and other late asthmatic reactions is not explained by this mechanism. Cromolyn therapy may reduce steroid dependency and side effects, but the subjectivity of steroid dosing makes documentation of this use difficult to prove.[39] Cromolyn has been most effective for young, mildly asthmatic patients and as a single agent for preventing exercise-induced asthma. An adequate trial of cromolyn requires three to six weeks of therapy. Cromolyn can be administered by a turboinhaler (using 20-mg capsules), nebulizer (using a 1% solution), or an MDI (1 mg per puff). The MDI dose is two puffs four times a day. Side effects (cough, throat irritation, mild bronchospasm) are minor and are mainly noted with the capsule or turboinhaler.

Management Approaches

Suggested approaches to the bronchodilator management of asthma in some clinical settings are listed.

Emergency Plan for Patients

Every patient should have a written treatment plan to include current medications, how to reach physician or emergency services, and the emergency use of oral steroids if there is a delay in getting to a physician or an emergency department.

Acute Decompensation in an Emergency Department

The first recommendation listed is efficacious and usually safe, but one of the other three may be needed if the patient cannot use an aerosol:

- Inhaled β-agonist by MDI, two puffs; may be repeated every five minutes or until side effects appear; *or*
- Epinephrine (1:1,000), 0.15 ml subcutaneously; dose may be repeated once; *or*
- Terbutaline, 0.25 mg (0.25 ml) subcutaneously; may be repeated once after 20 to 30 minutes; *or*
- Epinephrine suspension (1:200), 0.15 ml subcutaneously.

Failure to alleviate an attack within 30 to 60 minutes will require the addition of intravenous theophylline and steroids. Aminophylline should be given by intravenous load as follows, depending on recent theophylline ingestion: 6 mg per kg if no recent theophylline usage over 15 minutes; *or* 3 mg per kg if theophylline may have been used recently, or if taken in a reduced dosage; aminophylline is not needed if patient has been taking theophylline regularly. The steroids to be considered are prednisone, 1.0 mg per kg orally, *or* methylprednisolone sodium succinate, 1.0 to 2.0 mg per kg intravenously.

If extended observation or hospital admission is anticipated, an aminophylline infusion, 0.7 mg per kg per hour, should be started and β-agonist aerosol therapy, two puffs every four to six hours, maintained.

During Hospital Stay

In the hospital the following regimen should be continued:

- Aminophylline, 0.7 mg per kg per hour by infusion; daily blood concentrations at least for the first two days to adjust infusion rate;
- β_2-agonist aerosol, two puffs every four to six hours;
- Methylprednisolone, 0.5 to 1.0 mg per kg twice a day.

For patients with respiratory failure manifested by hypoxemia, persistent hypercapnia, and acidosis, anticholinergic agents or higher doses of steroids can be administered, but intubation, mechanical ventilation accompanied by sedation, or general anesthesia may be necessary.[40]

As the patient stabilizes, a switch to oral therapy should be started: theophylline, sustained-release, 6 mg per kg twice a day; β_2-agonist aerosol, two puffs every four to six hours; prednisone, 0.5 mg per kg per day orally, with tapering tailored to each patient as dictated by severity, chronicity of disease, and prior steroid therapy.

Ambulatory Care

The outpatient guideline for bronchodilators is more personal and perhaps arbitrary. Two contrasting styles are presented, realizing that physicians and patients may prefer different regimens.

- Stepwise therapy would begin with a β_2-agonist (tablet only if aerosol cannot be used) or theophylline, adding the other agent if needed: β_2-agonist aerosol, two puffs every four to six hours; *or* theophylline sustained-release, 6 mg per kg twice a day. In patients with mild asthma, a physician may try giving a "24-hour" preparation of theophylline, 10 to 12 mg per kg at bedtime.
- Some patients may require a combined use of sustained-release theophylline, 6 mg per kg twice a day; β_2-agonist aerosol, two puffs every four to six hours; and oral or aerosol steroids—prednisone, 0.5 mg per kg a day. The key to this approach is the need to carefully decrease the dose or withdraw steroid therapy as rapidly as possible to prevent steroid dependency.

Relegated to second-line therapy are anticholinergics, steroid aerosol, and cromolyn, although each may be used as primary therapy in some patients.

Exercise and the Athlete

Avoiding strenuous exercise in cold, dry air is often a necessity for many patients with asthma but is a difficult choice for a dedicated jogger, skier, or cyclist. Using a paper mask, nose breathing, and prolonged deceleration during a lengthy run and aerobic training are sometimes useful aids in addition to medication to prevent exercise-induced asthma. The inhaled β-agonists are effective agents to prevent or ameliorate the symptoms of exercise-induced asthma on an ongoing basis but can also be administered effectively 15 to 30 minutes before an outdoor race or game. Cromolyn in a metered-dose inhaler is probably the second (first in some persons) choice and, if given 30 minutes before vigorous sporting activity, will reduce bronchospasm and not produce tremor or chronotropic side effects. Oral medications, including oral β_2-agonists, theophylline, and calcium channel blockers, are preventive therapy, but muscle tremor, accelerated heart rate, and nausea may occur and interfere with sporting performance. Some persons have to alter their exercise style or location to indoor sports. Swimming may be an acceptable alternative for asthmatic exercise enthusiasts. All persons with asthma should continue some exercise such as walking to maintain respiratory muscle strength.

Pregnant Patients

Asthma may abate, stay the same, or worsen during pregnancy. Major goals include preventing respiratory decompensation in the mother and protecting the fetus. The first goal might require using more than one antiasthmatic medication, whereas the second would require a minimal use of medication. Although many of the newer β-agonists, theophyllines, and aerosol steroids have not been tested in large populations of pregnant patients, they have had five to ten years of scrutiny in this country and abroad.[41] For most patients their usual medication regimen can be continued with the following precautions:

- Limit the use of all antiasthmatic medications during the first trimester.
- Aerosol delivery of β_2-agonists and steroids may provide the best protection with the fewest side effects. Beclomethasone would be the first steroid choice because triamcinolone and flunisolide have had less scrutiny.
- Short courses of steroids may give the quickest relief of exacerbations with minimal effects on the fetus.
- Oral and subcutaneous β-agonists given late in pregnancy may inhibit labor and cause pulmonary edema.

NOTE: Additional references on the management of asthma are available from the author.

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Current Status of Pancreas Transplantation

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Pancreas transplantation for the treatment of diabetes mellitus is being done with increasing frequency. Refined operative techniques, an improved immunosuppression regimen, and an earlier recognition of rejection have led to dramatic increases in both graft and patient survival rates. Preliminary data suggest that a functioning pancreatic allograft may arrest or reverse most of the complications of diabetes, although the effects on retinopathy remain controversial. Patients also acquire a strong sense of well-being after successful pancreas transplantation.

(Cook DW, Sasaki T: Current status of pancreas transplantation. West J Med 1989 Mar; 150:309-313)

Clinical pancreas transplantation for the treatment of diabetes mellitus is being used with increasing frequency. Between December 1966 and April 1987, a total of 1,157 pancreas transplants had been reported to the International Pancreas Transplant Registry, with 736 having been done since 1983.[1] The resolution of early technical problems and improved immunosuppression have enhanced graft survival. Morbidity and mortality rates have likewise been reduced.

A successful pancreas transplant achieves a more physiologic approach to the treatment of diabetes mellitus and may arrest the complications of diabetes. Patients also report a notable improvement in their sense of well-being.

Historical Aspects

Early investigation of the source and action of insulin led to the finding that a denervated pancreas allograft could autoregulate and maintain normoglycemia. Before the first clinical pancreas transplant in 1966, extensive experimental studies focused primarily on the technical aspects of transplantation.[2,3] A number of techniques were developed, and most were discarded. These early methods included partial pancreaticoduodenal allografts with external drainage and segmental and whole pancreas, duct-ligated allografts. Complications were frequent and included autodigestion, fistula formation, infection, and vascular thrombosis. There were no long-term successes. The present methods are now best classified as to whether segmental or whole organ transplantation is done and according to the method of exocrine secretion management.

Patient Selection and Evaluation

Most patients considered for pancreatic transplantation have type I (insulin-dependent) diabetes mellitus. Those who have had transplants fall into four groups: those with systemic complications such as retinopathy or neuropathy without renal involvement, patients without systemic complications of insulin-dependent diabetes but in whom metabolic control is difficult, patients with a previous kidney transplant, and those patients with end-stage renal disease and systemic complications who would benefit from simultaneous kidney and pancreatic transplants.[4-7]

Patients must be of a suitable age, generally 15 to 50, show ABO compatibility with a negative crossmatch, and lack physical evidence of far-advanced systemic complications such as gangrene of the lower extremities, severe gastroenteropathy, and significant coronary artery disease. Other contraindications to pancreas transplantation include the presence of active infections, malignancy, alcoholism or chemical dependency, and certain psychiatric illnesses.

All patients undergo extensive laboratory and physical examination including detailed neurologic, ophthalmologic, and cardiac evaluations. Because of the significant incidence of coronary artery disease in this patient population, considerable emphasis is placed on the cardiac evaluation. Most centers begin with noninvasive studies in asymptomatic patients and proceed to coronary angiography when results are positive or inconclusive. Some centers do angiograms on all candidates.[8,9] Abnormalities detected with coronary angiography may be treated with an angioplasty or coronary artery bypass graft before a pancreatic transplantation.

Donor Selection

In general, the criteria for selecting a pancreatic cadaver donor are similar to those used with kidney, heart, or liver donation. The donor must be clinically brain dead; be free of malignancy except primary brain tumors and possibly skin tumors; have no septic or chronic infectious process, hepatitis, or a positive titer for the human immunodeficiency virus; be younger than 60 years of age; and have no prolonged hypotension or asystole. In addition, other criteria specific for pancreas transplantation include no history of alcoholism or chemical dependency, no metabolic or endocrine-related coma, no evidence of intra-abdominal or pancreatic trauma, and normal pancreatic function with no family history of diabetes. Mild hyperamylasemia and hyperglycemia are not contraindications to pancreas donation since amylase and glucose levels may be elevated due to resuscitative efforts rather than pancreatic damage.

Immunologic advantages have led to the use of segmental grafts from living related donors. Sutherland and co-workers have defined specific criteria for living related donor selection. These include normal glucose tolerance indices; absent islet cell antibodies; a sum of the insulin values at 0, 60, 120, and 180 minutes during the cortisone-stimulated glucose tol-

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erance test of greater than 90 μU higher than the sum of corresponding values of the standard tests; and a sum of 1- and 3-minute insulin values during an intravenous glucose tolerance test of greater than 80 μU. Living related donors must also be at least ten years older than the recipient was when diabetes started, and the recipient must have had diabetes at least ten years before transplant. Using these criteria, Sutherland and associates have not reported abnormal results on oral glucose tolerance tests postoperatively or donor deaths.[7]

Pancreas Harvest and Preservation

The harvest and preservation of the pancreas is one of the most important aspects of transplantation. The transplant team must have a well-defined, systematic approach for retrieving more than one organ. To facilitate this, several techniques have been devised. Some involve meticulous dissection and isolation of each organ, while others stress an en bloc approach. To avoid excessive handling, which may aggravate graft edema and contribute to graft malfunction, a "no touch" technique of pancreatic harvest has been advocated.[8]

In most instances, the donor heart and kidneys are harvested concurrently. Procuring the liver, however, usually limits the procedure to segmental pancreas removal because the portal vein and celiac axis are used for both liver and whole pancreas transplantation. Modifications in technique may permit whole pancreas retrieval, but, in general, segmental grafts are harvested in liver donors.

A segmental graft consists of the tail and body of the pancreas based on a vascular pedicle of the splenic vessels or the portal vein and celiac axis. When the liver is harvested concurrently, the vascular pedicle is based solely on the splenic vessels. The whole pancreas graft is based on the portal vein, celiac axis, and superior mesenteric artery. In addition, a button of duodenum containing the papilla of Vater or the entire duodenum is harvested en bloc with the whole pancreas.

The pancreas is especially susceptible to warm ischemia. Cold perfusion usually with a Ringer's lactate solution is therefore initiated in situ after the aorta and inferior vena cava are cannulated or immediately after removal. Low-pressure perfusion with Collin's solution or a similar cold storage solution is continued ex vivo, and hypothermic storage (4°C) is maintained until transplantation.

Once in cold storage, the pancreas graft is prepared for transplantation. Lymphatics are ligated with fine sutures, the vessels are further dissected and prepared for anastomosis, and the exocrine duct is prepared.

The preservation time is optimally less than six hours. Cold storage of longer than 12 hours, however, has been compatible with normal graft function.[10] This relatively short storage does not allow for human leukocyte antigen typing. Recipient selection, therefore, is based on ABO compatibility.

Surgical Technique

Pancreas transplants may be categorized by whether a segmental or a whole organ graft is used. Classification is further defined by the site of transplantation and the method used to manage the exocrine duct.

Segmental grafts are commonly placed extraperitoneally or intraperitoneally in the pelvis with vascular anastomosis to the iliac vessels (Figure 1). The exocrine duct may be occluded with neoprene or drained into the jejunum or urinary bladder. Less common variations include drainage into the stomach and placing the graft in the groin with the duct occluded. Whole organ grafts are also placed in the pelvis using similar techniques. The most common forms of exocrine drainage are Roux-en-Y pancreaticojejunostomy (enteric drainage; Figure 2) and pancreaticocystostomy (bladder drainage; Figure 3).

Segmental grafts are more frequently used in Europe, constituting 90% of cases, while in North America 70% are whole organ transplants. Methods of duct management also vary. Urinary drainage accounts for about 70% of cases in North America and duct occlusion, usually with neoprene, 56% of cases in Europe.[1] The ideal pancreatic mass for transplantation and the best surgical technique remain controversial.[11] Further studies are necessary to elucidate these problems.

Immunosuppression

Agents currently used for immunosuppression and for the treatment of allograft rejection in pancreas transplantation include cyclosporine, azathioprine, prednisone, antithymocyte globulin, antilymphocyte globulin, and OKT3 or a similar monoclonal antibody.

The combination of prednisone and azathioprine was the mainstay of immunosuppression before the development of cyclosporine. Successful results were limited, however. The addition of cyclosporine enhanced graft survival.[12] Cyclosporine used alone achieves results comparable to the combination of azathioprine and prednisone, but when used in combination with azathioprine, prednisone, or both, the results are significantly improved.[10] Most current regimens use multidrug combinations, primarily triple-drug therapy with

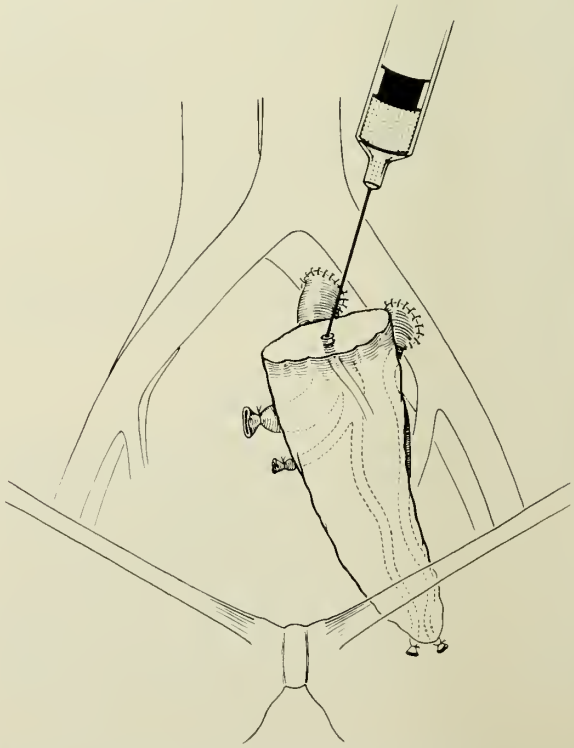

Figure 1.—A segmental pancreas allograft is shown with the occluded exocrine duct placed in the pelvis with vascular anastomosis to the iliac vessels.

cyclosporine, prednisone, and azathioprine. In addition, Sollinger and colleagues have reported a further improvement of graft survival by adding antilymphocyte globulin to the triple-drug regimen.[13] The synergistic effect noted with multidrug use allows the administration of lower doses of individual drugs, thus lowering the risks of detrimental effects. Immunosuppression may also be tailored to each patient to a certain degree.

As in renal transplantation, adjuvant methods of immunosuppression continue to be evaluated. A blood transfusion is often given preoperatively, although the benefits are not defined in pancreas transplantation. The donor spleen has been included with the pancreas allograft in an attempt to improve immunologic acceptance, but substantial graft-versus-host disease has resulted, and no immunologic benefit has been conclusively shown.[14-16] Other adjunctive measures that have been or are currently under investigation include selective depletion of passenger leukocytes in the allograft, recipient lymphoid irradiation, or splenectomy, plasma exchange, and thoracic duct drainage.[17-19]

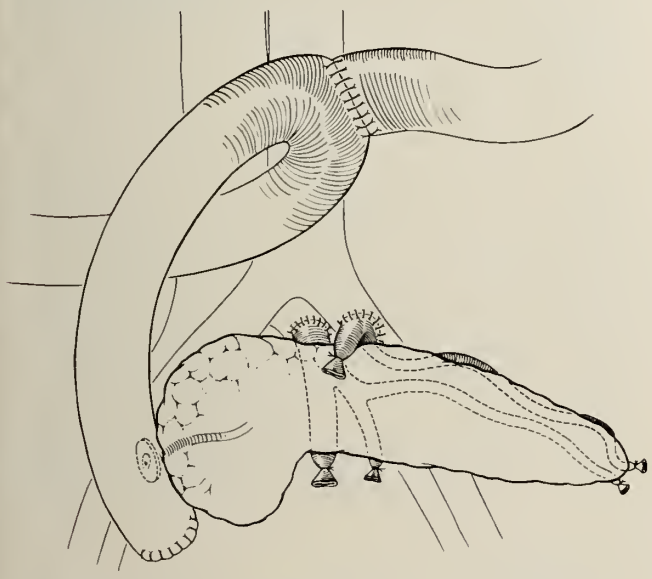

Figure 2.—A whole pancreas allograft is placed in the pelvis with Roux-en-Y duct drainage and vascular anastomosis to the iliac vessels.

Figure 3.—A whole pancreas allograft is shown using pancreaticocystostomy with vascular anastomosis to the iliac vessels.

Rejection is most commonly treated with the pulsed administration of high doses of steroids or courses of antilymphocyte or antithymocyte globulin. Monoclonal antibodies such as OKT3 or similar agents are also used to treat primary rejection episodes, although many centers reserve their use for recurrent rejection.

Postoperative Management

A pancreas transplant recipient requires certain management considerations in addition to routine postoperative care. For example, a significant incidence (approximately 11%) of graft thrombosis and subsequent graft failure necessitates the use of anticoagulation in the postoperative period.[10] This is accomplished in many centers by the use of low-molecular-weight dextran, aspirin, or dipyridamole (or a combination of these) and may range to full anticoagulation with the administration of heparin followed by warfarin sodium.

Occasionally when a portion of duodenum is included with the whole pancreas graft and drained into the urinary bladder to facilitate exocrine drainage, a metabolic acidosis results due to bicarbonate loss. This may require maintenance bicarbonate supplements.[6]

In addition to these measures, some investigators think that graft survival is enhanced by "resting" the newly transplanted pancreas in the immediate postoperative period. Small doses of insulin are therefore given to keep plasma glucose levels at less than 8.3 mmol per liter (150 mg per dl) while the patient is receiving intravenous fluids.[7,9,20] Somatostatin may also be given to reduce graft edema and exocrine secretion.[9,21]

Antibiotics, usually second- or third-generation cephalosporins or a semisynthetic penicillin, are often administered perioperatively and for as long as five days after the operation. Nasogastric suction and a nothing-by-mouth status are maintained until the postoperative ileus resolves. If prolonged (longer than a week) ileus is expected or if nutritional deficiencies are evident, hyperalimentation is initiated.

Blood glucose levels are measured as frequently as hourly in the immediate postoperative period, and blood chemistry levels are measured daily. Glucose tolerance tests are done and metabolic profiles are determined as needed. Patients are instructed on monitoring their blood glucose, weight, and temperature at home and are observed as outpatients at least weekly in the immediate postoperative period.

Diagnosing Rejection

The recognition of rejection in a pancreas recipient is often difficult. The clinical findings of rejection, which include fever, graft tenderness, abdominal pain, ileus, malaise, and leukocytosis, are not consistently present and may be found with graft pancreatitis, recurrent disease, vascular thrombosis, and intra-abdominal infections. Furthermore, methods available to assist in the diagnosis of rejection may be limited by the type of exocrine management.

The mainstay of diagnosis has been an elevation of fasting serum glucose levels. Unfortunately, this is a relatively late

finding and in most patients with hyperglycemia, graft function continues to deteriorate despite antirejection therapy.[22] Exocrine function, however, has been shown to be a sensitive marker of graft rejection.[23,24] Using certain techniques of exocrine management, these secretions may be easily and reliably assessed. Enteric drainage techniques allow these secretions to be quantified, but more accurate daily determinations of amylase levels are made using the urinary bladder drainage technique. Reductions of urinary amylase levels measured by these techniques have been shown to correlate well with early graft rejection. Serum amylase levels, however, are difficult to interpret and are of little use in diagnosing rejection.[25]

Other means of recognizing pancreas graft rejection are being investigated. Various serum and urinary markers of graft function have been identified, although to date their use has met with limited success. Graft imaging techniques such as ultrasonography, nuclear magnetic resonance, and radionuclide scans may provide useful information, but they also require further refinement.

The most definitive method of diagnosing rejection in the pancreas graft is open biopsy. This, however, requires a surgical procedure that is associated with pancreatitis, leak, and fistula formation, creating significant risk for these patients. It is therefore infrequently done.

In a patient with a simultaneous kidney-pancreas transplant, the markers of kidney rejection precede those associated with pancreas rejection. Experimental studies have shown that mononuclear cell infiltration occurs simultaneously with rejection in both organs. Islet sparing is noted early in the course of rejection, however.[26] In most instances, elevations in blood urea nitrogen and creatinine values occur earlier than hyperglycemia. Prompt treatment following evidence of kidney rejection results in increased pancreatic graft survival.[13]

Results

The early results of pancreas transplantations were dismal. As recently as four years ago, the overall one-year rate of graft function was 23% and the associated three-month mortality rate 18%.[27] Improved immunosuppression, refined operative techniques, and the earlier diagnosis and treatment of rejection, however, have improved results dramatically. The rates of overall graft and patient survival reported to the pancreas transplant registry between 1983 and 1987 were 47% and 81%, respectively.[1]

Worldwide the number of segmental grafts far exceeds the number of whole organ transplants, while the three principal methods of duct management, occlusion and enteric and urinary drainage, enjoy equal popularity. Overall graft and patient survival rates for each method, however, show no statistical difference. A preservation time of less than six hours improves the rate of graft survival to a small but significant degree when compared with preservation times of more than six hours (46% versus 39%). Combination immunosuppression regimens with cyclosporine, azathioprine, and prednisone also are associated with a higher rate of graft survival when compared with using cyclosporine without azathioprine or azathioprine without cyclosporine. No detrimental effects on patient survival are noted with the multidrug protocols.[1,10]

Graft failure is most often due to rejection (40%), although technical problems, including a 10% to 15% incidence of vessel thrombosis, account for 20% to 25% of graft losses.[10] In addition, major complications including pancreatitis, fistula formation, exocrine leak, and infection occur in as many as 50% of patients. It is anticipated, however, that further improvements of technique and immunosuppression will lower the incidence of these problems.

Recently Sollinger and co-workers have reported overall graft and patient survival rates of 73.1% and 95.6%, respectively, at one year. They use whole organ grafts with urinary bladder drainage and quadruple-drug immunosuppression with prednisone, cyclosporine, azathioprine, and antilymphocyte globulin.[13] They believe that bladder drainage of exocrine secretions has led to these superior results because the use of this technique has resulted in fewer complications and has allowed for the earlier diagnosis and treatment of rejection. Similar results have been reported by others using this technique.[8,28]

With this improved graft survival, evidence is mounting that pancreas transplantation may lead to a reversal or arrest of the complications of diabetes. Serial biopsy specimens taken one to four years after simultaneous kidney-pancreas transplants show no renal diabetic changes, whereas kidneys transplanted alone in a diabetic patient may show diabetic nephropathy as early as 30 months after transplantation.[29] This suggests that a functioning pancreatic graft may prevent renal changes associated with diabetes. Nerve conduction studies have documented improvement after successful transplantations, and most patients have reported symptomatic improvement.[4-7,9,20,29-31] Visual acuity may also stabilize, although early results are inconclusive.[4-7,9,20,29,31] Prospective studies are underway to further evaluate the metabolic and physiologic effects of pancreas transplantation.

Conclusions

Graft survival rates now approach those of other solid organs, and other significant gains have been made. Surgical techniques have been refined, and combination immunosuppression has improved graft survival without adversely affecting patients' morbidity and mortality. As a result, the metabolic and physiologic benefits of pancreatic transplantation are being realized.

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Editorial Comment

Coming of Age for Pancreas Transplantation

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The discovery of insulin in 1922 changed type I diabetes mellitus from an acute, rapidly fatal disease into a chronic, incurable disease.[1] Insulin administration can prevent ketoacidosis, but no method of exogenous administration can restore a normal metabolic state.[2] Twenty years after the onset of clinical disease, more than half of patients with type I diabetes mellitus have serious secondary complications involving the eyes, nerves, or kidneys.[3] Diabetes is the leading cause of new cases of blindness in the United States, accounts for 25% of all cases of end-stage renal failure, and patients with diabetes are five times as likely to require an amputation and two times as likely to have heart disease as the general population.[4]

Efforts to develop a closed-loop insulin pump coupled to a glucose sensor, mimicking a beta cell in which the secretion of insulin is regulated on a minute-to-minute basis, have so far not been successful.[5] Likewise, one of the original ideas of Banting, as described by Bliss,[6] to transplant free grafts of insulin-producing tissue (islets) has not materialized as a practical clinical option.[7] To date, the only form of total endocrine replacement therapy that has been successful in the treatment of diabetes is pancreas transplantation as an immediately vascularized graft.

In this issue, Cook and Sasaki review the current status of pancreas transplantation. The first clinical pancreas transplant was done in 1966.[8] In recent years there has been a dramatic increase in the number of cases and in the success rate.[9] As pointed out in the review, a pancreas transplant, when successful, establishes a euglycemic, insulin-independent state. The only effort required by the patient to maintain this state is to take the immunosuppressive drugs necessary to prevent rejection. Although there are surgical risks, improvements in techniques over the years have made pancreas transplantation a safe procedure.

The need for long-term immunosuppression and the side effects of the antirejection drugs are the main drawbacks to pancreas transplantation. Since patients with end-stage diabetic nephropathy who receive a kidney transplant are already obligated to immunosuppression, the majority of pancreas transplant recipients have been in this category. There are very few reasons not to do pancreas transplant in this group of patients, because the immunosuppressive management is no different after a kidney and a pancreas transplant than after a kidney transplant alone. Doubly grafted patients in whom both organs function have the added benefits of insulin independence, the prevention of the recurrence of diabetic nephropathy in the transplanted kidney,[10] and at least the potential for a salutary effect on some preexisting secondary complications of diabetes.

Pancreas transplantation is increasingly being applied to patients without uremia who have not had a kidney transplant.[11] The patients selected for pancreas transplantation alone are those in whom complications of diabetes are, or otherwise would be, more serious than the potential side effects of antirejection therapy. The specific criteria for pancreas transplantation in this category of patients are being continuously redefined as strategies designed to minimize the side effects of immunosuppression evolve.[12] The current trend in immunosuppression for organ transplant recipients is to use several drugs with different modes of action at low doses, based on the findings that the synergism between the drugs is greater for their therapeutic (immunosuppressive) than for their toxic effects.[13] The regimen used in pancreas transplant recipients at the University of Minnesota Medical Center[14] and other centers[15] entails administering temporary courses of heterologous lymphocyte globulin or monoclonal antibody preparations for both induction immunosuppression and the treatment of rejection episodes; cyclosporine, azathioprine, and prednisone for both induction and maintenance immunosuppression; and corticosteroids for the treatment of rejection episodes. Variants of this regimen have been successful in preventing rejection of other solid organ transplants,[16] and data from the Pancreas Transplant Registry[17] and from individual centers[18] show such an approach to be associated with the highest graft and patient survival rates for pancreas transplant recipients as well.

Although a pancreas transplant may be successful in diabetic patients who have not yet shown a propensity to have secondary complications develop, there is no guarantee that the immunosuppressive drugs given to prevent rejection will not produce side effects more serious than what would have evolved from their basic disease. Thus, recipients for a pancreas transplant alone must be carefully selected.[19] At the University of Minnesota, the institution with the largest experience in this area,[20] almost all pancreas recipients have had at least early lesions of diabetic nephropathy with microalbuminuria, a situation that nearly always (without a pancreas transplant) leads to uremia. In these patients, if the progression of nephropathy is halted by a pancreas transplant, uremia is avoided with the added benefit of insulin independence. Again, the potential to favorably influence other complications exists. If the progression of uremia is not prevented, the recipient has still had the benefit of insulin independence, offsetting the slight risk of introducing immunosuppression earlier than what would have been required had the patient waited until the need for a kidney transplant was absolute.

The progression of established nephropathy after a pan-

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creas transplant has been uncommon,[20] and results of preliminary studies at the University of Minnesota show that a successful pancreas transplant can halt the progression of microscopic renal lesions if done early enough in the course of the disease.[21] In seven nonuremic patients with successful pancreas transplants who underwent biopsies of their native kidneys at the time of and two years after the transplant, the mean glomerular mesangial volume was significantly less at the follow-up compared with that of the baseline biopsies. Expansion of the mesangium is a classic lesion of diabetic nephropathy that correlates with impaired renal function. Thus, a decrease in the mesangial volume signifies a reversal of a lesion specific for diabetic nephropathy. Although the improvement in the morphologic features of the diabetic kidney following pancreas transplantation was achieved at the expense of cyclosporine nephrotoxicity, the detrimental effect of cyclosporine use on renal function did not appear to be progressive. In the seven patients of the study cited,[21] the mean creatinine clearance declined from a pretransplant value of 90 ml per minute to a posttransplant value of 60 ml per minute; the decline in creatinine clearance occurred early (three months), however, and thereafter renal function stabilized. Studies in other cyclosporine-treated recipients of pancreas transplants who were not uremic and did not receive kidney transplants, observed for as long as five years, have also shown that renal function stabilizes in the long term.[22]

Pancreas transplantation also appears to have a beneficial effect on other diabetic complications, depending on the stage of the lesion at the time of transplantation. In a study of diabetic retinopathy at the University of Minnesota, approximately 30% of recipients with successful pancreas transplants and retinopathy beyond the background stage progressed to a more advanced stage of retinopathy by two years after the transplant, no different than that in a control group of patients whose grafts failed early (within three months).[23] Thereafter, however, retinopathy remained stable in the patients with successful grafts, while deterioration was continuous in the control group.[23]

Neuropathy, as pointed out by Cook and Sasaki, either decreases or stabilizes after successful pancreas transplantation,[24] at least in nonuremic persons.[20] Detailed studies in pancreas recipients at the University of Minnesota have shown increases in nerve conduction velocities by one year after a successful pancreas transplantation (W. R. Kennedy, X. Navarro, F. C. Goetz, D. E. R. Sutherland, and J. S. Najarian, "Effects of Pancreas Transplantation on Diabetic Neuropathy," unpublished manuscript, 1988). By three years, motor and sensory indices of function are significantly better in patients with functioning grafts compared with controls whose grafts failed early, and the decline in autonomic nerve function has halted in the functioning while continuing in the failed pancreas transplant group.

There is no reason for the success rate with pancreas transplantation not to continue to improve. Although the application to nonuremic patients who have not had a kidney transplant is largely limited to the subsets with either extremely labile diabetes or early nephropathy and will remain so until completely effective, nontoxic antirejection treatments are available, the addition of a pancreas to a kidney transplant in the management of uremic diabetic recipients of kidney transplants is becoming routine at many centers.[25-31] The results of pancreas transplantation are also best when carried out simultaneously with a kidney transplant. The registry figures cited in the review reflect the results worldwide as the procedure has evolved, but the individual centers with the largest recent experiences with simultaneous pancreas and kidney transplants report one-year patient survival rates of more than 90%, kidney graft survival rates of 70% to 90%, and pancreas graft survival rates of 60% to 80%.[25-31]

For pancreas transplants alone, the graft survival rates are less good, primarily for immunologic reasons. Only pancreas graft function can be monitored in this situation, while in doubly grafted patients both the kidney and pancreas can be monitored; if both came from the same donor, a rejection episode of the kidney, early diagnosed by a rise in serum creatinine levels coupled with a kidney biopsy, may mirror ongoing but as yet undetectable rejection in the pancreas, and treating kidney rejection automatically treats that of the pancreas.[32] In contrast, for nonuremic recipients of pancreas transplants alone, the rejection rate is not only higher, the diagnosis is made later than in doubly grafted patients who also are uremic at the time of transplantation, and uremia itself is immunosuppressive.[33] The results of pancreas transplantation alone have dramatically improved with the bladder drainage technique. A decline in exocrine function is manifested by a decrease in urinary amylase activity.[15,34] This precedes hyperglycemia, allowing for earlier diagnosis and treatment of rejection episodes.[36] Using the bladder drainage technique, current one-year patient and graft survival rates in nonuremic recipients of pancreas transplants at the University of Minnesota who did not have kidney transplants are 96% and 48%, respectively.[20]

The review by Cook and Sasaki is comprehensive, but by the very nature of publishing is already out of date. Hence, some recent statistics and comments pertinent to each of the sections in their review will be added here. The most recent analysis of the Pancreas Transplant Registry data included 1,549 cases as of June 30, 1988.[36] Of these, 1,149 were done since 1983 and 762 since 1985. In this latter group, the one-year actuarial patient and graft survival rates were 88% and 55%, respectively, significantly higher than in previous eras.

Historical Aspects

Historically, there are many milestones. The first large series of pancreas transplants was that of Lillehei and associates carried out at the University of Minnesota between 1966 and 1973.[37] Only one patient in this early series of 14 cases survived with a functioning graft for more than a year, but the ability of a pancreas transplant to establish a normoglycemic, insulin-independent state was clearly demonstrated. Numerous investigators have contributed to the development of surgical techniques. The introduction of the nonphysiologic method of duct injection with a synthetic polymer by Dubernard and colleagues in 1976 made pancreas transplantation a safe procedure and embraced the concept of a pure endocrine graft.[38] The urinary drainage method was introduced by Gliedman and co-workers as early as 1971, in which the recipient's ureter was anastomosed directly to the pancreatic duct,[39] and this approach was later (1982) modified by Sollinger and colleagues with direct anastomosis to the bladder,[15] eliminating the requirement to sacrifice a kidney and making the exocrine drainage procedure technically easier. The introduction of cyclosporine by Calne and White in 1978 contributed to improved results with all organ transplants,[40] the pancreas being no exception. Thus, today several satis-

factory techniques are available for pancreas transplantation, and immunosuppression modalities have evolved that are safe and effective.

Patient Selection and Evaluation

It seems clear that diabetic patients with uremia who are candidates for a kidney should almost always be considered for a pancreas transplant as well, since immunosuppression is obligatory and the only risk is surgical. Debate continues on which nonuremic patients with diabetes who have not had a kidney transplant are candidates for a pancreas transplant, but guidelines are available.[19] Our approach at the University of Minnesota is to select patients with either extremely labile diabetes as an indication in and of itself, or patients with progressive secondary complications that include early nephropathy.[20]

Donor Selection

Nearly all brain-dead cadavers who are appropriate for kidney, heart, or liver donation are suitable as pancreas donors.[41] There is, however, some evidence that pancreas grafts taken from donors who became hyperglycemic through resuscitative efforts have lower one-year function rates than those taken from donors who remained normoglycemic throughout the stressful procurement period.[42]

Living related pancreas donation is generally reserved for patients in whom cytotoxic antibodies to a high percentage of the general population have developed (from previous blood transfusions, pregnancies, or transplants). It is difficult to find a cadaver donor to whom there is a negative crossmatch for these patients. Often, such persons will have negative crossmatches against living relatives. If the relatives meet the criteria as outlined in regard to plasma insulin levels during preoperative stimulating tests, the donors will remain metabolically normal after donation, but if secretory tests show insulin levels below the range, glucose tolerance test results may be abnormal following hemipancreatectomy.[43] The incidences of complications from operating on a normal pancreas in living donors has been low.[44] Besides the advantage of using a relative when this is the only possible donor, the graft functional survival rates are significantly higher over the long term with related as opposed to cadaver donor pancreas transplants.[29,45]

Pancreas Procurement and Preservation

A pancreas can be retrieved with all other organs from a cadaver, including the liver. Most groups now routinely procure whole pancreas grafts from liver donors, preserving blood flow to the head of the pancreas through the superior mesenteric-inferior pancreaticoduodenal arcade and to the tail of the pancreas through the splenic artery.[46] If the celiac axis is retained with the liver, the splenic and superior mesenteric arteries of the pancreas can be joined directly or by a Y graft using the donor iliac arteries. An adequate portion of portal vein can be retained with both the pancreas and the liver by dividing the portal vein at its midpoint between the pancreas and liver, and an extension graft for the vein is usually not necessary.

It is important to emphasize that the problems with pancreas preservation have largely been solved. Two solutions, a silica gel fractionated plasma developed at the University of Minnesota[47] and an intracellular electrolyte formulation containing lactobionate, hydroxyethyl starch, and raffinose developed at the University of Wisconsin,[48] have successfully preserved pancreas grafts for as long as 72 hours.[49,50] Both of these solutions have allowed human pancreas grafts to be stored for more than 24 hours with a successful outcome.[51-53] Collin's solution, originally intended for the kidney, is definitely inferior. The latest analysis of registry data shows no difference in functional survival rates for grafts subjected to more than 24 hours preservation times versus shorter times.[35] Thus, the logistics of pancreas transplants are at a point where human leukocyte antigen (HLA) matching could be used in selecting the most appropriate recipients for grafts from individual cadaver donors.[54]

Surgical Technique

Most pancreas transplants done in the United States today are of the whole gland with exocrine drainage through the urinary bladder. A much more eclectic approach is taken in Europe.[17] The registry does not show any overall difference in outcome according to surgical technique or size of the graft.[17] In nonuremic recipients of cadaveric pancreas transplants alone, however, urinary drainage has clearly been associated with superior results at the one institution with an extensive experience with all of the commonly used duct management techniques.[29]

The immunosuppression used in pancreas transplant recipients is similar to that used for recipients of other solid organ allografts.[16] Cyclosporine and azathioprine are more synergistic for their therapeutic effects than for their toxic effects,[13] and most US programs use these drugs in combination with prednisone to treat their recipients. As pointed out in the review, antilymphocyte globulin or a monoclonal antibody such as OKT3 can be used for inducing immunosuppression as well as to treat rejection episodes. All current regimens are nonspecific, however, and pancreas transplantation will not be widely applied until completely effective, nontoxic pharmacologic regimens are available or until measures that suppress a specific immune response can be applied clinically. The adjunctive measures mentioned in the review that have this aim remain investigational.

Postoperative Management

Although numerous protocols have been used in an attempt to reduce the relatively high incidence of graft thrombosis, there is no evidence that anticoagulation is effective. Many institutions do not use anticoagulation, and the incidence of thrombosis appears to be decreasing. The relatively high incidence in the past may have been due to poor preservation techniques.

Diagnosing Rejection

As pointed out in the review, the diagnosis of rejection can be difficult. In recipients of simultaneous pancreas and kidney transplants, rejection in the kidney most likely mirrors ongoing rejection in the pancreas at a stage where reversal is possible. For those not having a kidney transplant, however, a marker other than glucose is needed because hyperglycemia signifies irreversible rejection in most cases. For this reason, the bladder drainage technique should be used in this group.[20] A decline in urinary amylase levels nearly always precedes the rise in plasma glucose values, and treatment based on a decline in urinary amylase will reverse the rejection process.[35]

Prospects

There is no reason the progressive improvement in pancreas transplant results will not continue. Certainly for uremic diabetic patients who are candidates for a kidney transplant, the addition of a pancreas does not have a detrimental effect on patient and kidney graft survival rates, and more than 60% of the patients will be free of insulin dependency and normoglycemic over the long term.[22,26-31,36] Thus, this option should be offered to most uremic diabetic patients. For the group of nonuremic patients who do not have a kidney transplant, pancreas transplantation will continue to be restricted to those patients who have complications of diabetes that are, or otherwise will be, more serious than the side effects of the antirejection treatment. When problems of rejection are solved, pancreas transplantation should be applicable to the entire spectrum of patients with type I diabetes.

There should be a sufficient number of donor pancreases available to treat all of those who would benefit. The annual incidence of new cases of type I diabetes mellitus (about 19,000) in the United States today[55] is only twice as high as the annual number of kidney transplants done.[56] Severe complications develop in only about half of type I diabetic patients in a lifetime.[4] Organs are currently procured from only a fraction of brain-dead cadavers who would be suitable as organ donors.[57] Because almost all donors of kidneys can also be donors of pancreases, it should be possible, as methods to prevent rejection improve, to treat all complication-prone diabetic patients who could benefit from a pancreas transplant.

The development of methods to specifically manipulate an immune response will facilitate organ transplants of all kinds. Eventually such sophistication in immunomodulation should lead to a decline in the incidence of insulin-dependent diabetes and a corresponding decline in the number of pancreas (or islet) transplants. Type I diabetes is an autoimmune disease in most cases,[58] and the pathologic autologous immune response to beta cells per se should be able to be "turned off" with the same facility as the autoimmune response to the histocompatibility antigens encountered in a transplant.

Until such an advance is made, however, pancreas transplantation will continue to be used to treat patients who have diabetes. Even without major changes in antirejection strategies, there are a large number of diabetic patients, both uremic and nonuremic, in whom the potential benefit of a pancreas transplant outweighs the current risks.[59]

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LARRY J. BARAFF, MD, *and* ERIK HEWLETT, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

Pertussis is a severe epidemic disease that causes significant morbidity and mortality in unimmunized children. It is now clear, however, that adults with atypical disease account for many of the cases and are often responsible for transmission to susceptible infants. Because of the extent of unrecognized pertussis in the adult population, mass pediatric immunization has been successful in controlling the disease in children but not in reducing the presence of the organism in the United States.

Pertussis immunization of children is associated with a high rate of side reactions and is temporally related to severe neurologic disease and death in infants. These events are often considered to be reactions, but available scientific evidence indicates that few, if any, are actually caused by pertussis immunization. Pertussis vaccine reactogenicity in adults is anecdotally considered to be worse than in children, but direct studies do not support that. In the context of current programs emphasizing adult immunization, consideration should be given to booster doses of diphtheria-tetanus-pertussis in adults, using component pertussis vaccines when they become available.

(Cherry JD, Baraff LJ, Hewlett E: The past, present, and future of pertussis—The role of adults in epidemiology and future control [Specialty Conference]. West J Med 1989 Mar; 150:319-328)

JAMES D. CHERRY, MD, MSc*: The World Health Organization recently estimated that there are 600,000 deaths a year due to pertussis; the vast majority of these deaths occur in unimmunized infants in developing countries.[1] During the period 1940 to 1948 in the United States when routine pertussis immunization was just getting under way, there were more deaths due to pertussis in infants than there were due to measles, scarlet fever, diphtheria, polio, and meningitis combined.[2] In recent years, there have been fewer than ten deaths per year in the US caused by pertussis.[3-6]

With this history, one might ask why we are discussing pertussis at this conference. Immunization in this country has been extraordinarily successful. Pertussis immunization, however, has not enjoyed sustained international success because of controversy relating to vaccine reactions. This controversy has been of such magnitude as to curtail or disrupt national programs in three major countries for more than a decade.[7-9] Only relatively recently has the controversy become a problem in the US.

Many physicians and much of the public at large are aware of the present pertussis vaccine controversy, but few understand what it is about. It must be said that it is more a legal, media, and political event than a scientific problem (ABC News, "20/20," February 5, 1985; NBC Broadcast, "DPT: Vaccine Roulette," 1982; S. Tompkins, "DPT: Vaccine's a Lifesaver—and a Hazard," *Fresno* [California] *Bee,* December 2-4, 1984; J. Hyman, "Toxic Vaccine Threatens Young Lives," *Rochester* [New York] *Democrat and Chronicle,* March 8-12, 1987).[10] Regardless of its nature, however, it is a threat to our present immunization program and the future control of pertussis in the United States. Because of this, new knowledge, and new vaccine technologies, it is worthwhile to reevaluate our pertussis immunization goals. Should and can we aim our sights at eradicating the causative organism, *Bordetella pertussis,* rather than preventing the disease, which is successfully being accomplished at the present time? If we use smallpox eradication as a model, our goal should be the eradication of *B pertussis,* in addition to preventing clinical pertussis. Compared with other vaccines that we currently use, the smallpox vaccine is inferior. Yet, smallpox was eradicated from the world in 1979 by a total international commitment and because the immunization program included adults as well as children. Because the pertussis vaccine is similar to the smallpox vaccine in that its

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ABBREVIATIONS USED IN TEXT

DT = diphtheria and tetanus toxoids vaccine, adsorbed [pediatric]
DTP = diphtheria and tetanus toxoids and pertussis vaccine, adsorbed
NCES = National Childhood Encephalopathy Study
SIDS = sudden infant death syndrome

protective effect is not lifelong,[11] a pertussis eradication program should involve booster immunizations in both adults and children.

In this conference, I review the history and epidemiology of whooping cough and the possible neurologic reactions to pertussis immunization, Dr Baraff presents data on common vaccine reactions, and Dr Hewlett reviews old and new vaccines and looks at the possibility of including adults in a future immunization scheme.

History, Epidemiology, and Disease

History

The first clearly described epidemic of pertussis occurred in 1578 in Paris.[12] During the Middle Ages, however, the treatment of illness in children with paroxysmal cough was recorded. In 1906 Bordet and Gengou reported isolating the causative organism of pertussis,[13] and throughout this century, an endemic and epidemic prevalence of pertussis has occurred in all populations in which children are unvaccinated.

Incidence of Disease

The pertussis attack rates for the United States and England and Wales are presented in Figures 1 and 2. The first point to note in these figures is that in both the US and England and Wales, the attack rates were not falling before the introduction and widespread use of pertussis vaccines. The mean attack rate for the prevaccine era in this country was 157 cases per 100,000 population. As a result of immunization, the pertussis attack rate in the United States decreased to less than 1 case per 100,000 population. In England and Wales, the pertussis attack rate also fell with the widespread use of pertussis vaccine, but following a decrease in vaccine usage from about 80% to 30%, epidemic pertussis reoccurred in 1977 to 1979, as is seen in Figure 2. Although some have claimed that the incidence of pertussis was falling before pertussis immunization was widely used,[14] there is no evidence to support this idea. It would appear from the epidemic curves in both the US and England and Wales that the incidence of pertussis relates directly to the immunization level in the population.

An important point to note in Figures 1 and 2 is the cyclic nature of pertussis. Fine and Clarkson in England noted that pertussis epidemics occurred about every three years and that, importantly, this pattern was the same in the prevaccine and vaccine eras.[15] I have noted a similar national epidemic pattern in the US.[16] In contrast to the pertussis epidemic cycle interval, which was not changed by widespread immunization, the epidemic cycle interval of measles changed dramatically in the United States following the widespread use of measles vaccine in 1966.[17] Before 1966, there was a yearly national cycle of measles in the United States, whereas after 1966 the next epidemic did not occur until 1971 and then again in 1977. The importance of this difference between the control of measles and pertussis through universal childhood immunization is that these observations indicate that with measles the circulation of the causative virus was reduced by immunization, but with pertussis the organism prevalence in the community was similar in both the vaccine and prevaccine eras. Today whooping cough in children is being effectively controlled by immunization, but the circulation of *B pertussis* is apparently continuing at a rate similar to that in the prevaccine era.

Pertussis has always been considered a disease of young children. Table 1 shows the distribution of cases of pertussis by age group in different time periods in the prevaccine era in Massachusetts, in England and Wales, and in the United

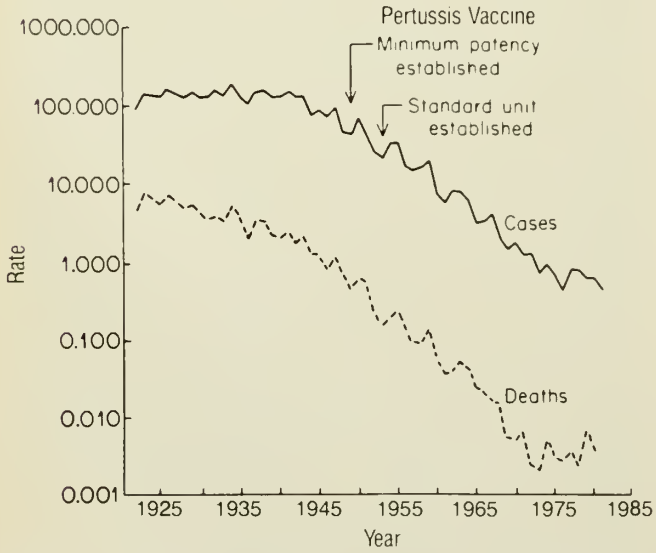

Figure 1.—The graph shows the reported cases of pertussis and deaths attributed to pertussis per 100,000 population by year in the United States, 1922 to 1981 (from Centers for Disease Control[3(p54)]).

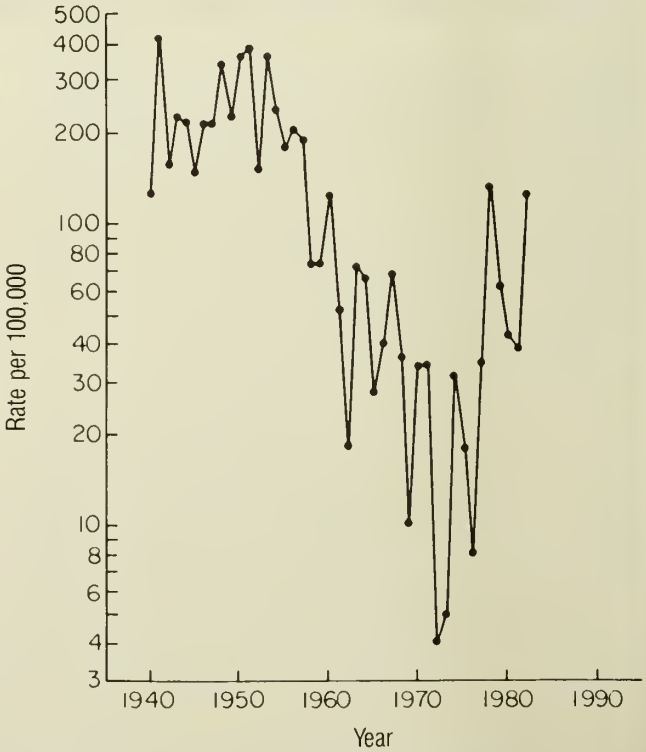

Figure 2.—The graph shows the pertussis attack rate by year, 1940 to 1982, in England and Wales (modified from Cherry[16(p12)]).

States during the present decade. In the prevaccine era in both this country and England and Wales, about 10% of cases occurred in the first year of life and 95% of cases occurred before 10 years of age. In the vaccine era in England and Wales, the same percentage distribution persisted (Table 1).[16] In contrast, in the US almost half of the cases are now being reported in infants and, in 1984 and 1985, 16.5% of the cases were in persons 15 years of age and older. The major difference in the percentage distributions by age in the vaccine era between the US and England and Wales is most probably explained by the fact that in England and Wales, immunization consists of only three doses of vaccine during the first year of life, whereas in the United States two additional doses of vaccine are given at 18 months and at 5 years of age. The high rate of infection in 5- to 9-year-old children in England and Wales as compared to the rate in similar-aged children in the US is due to illness in previously vaccinated children.

The increased percentage of cases in those 15 years of age and older in 1984 and 1985 as compared with 1978 to 1981 is difficult to explain. Most likely it is due to an increased awareness of pertussis caused by the recent medical and public media attention.

In the US there have been several nosocomial outbreaks of pertussis among hospital staff.[18-22] In these outbreaks the staff members have become infected from patients or their mildly ill parents.

Another point that needs to be addressed is the claim that the epidemic that occurred in Great Britain beginning in 1977 was exaggerated because physicians expected pertussis to occur owing to decreased vaccine usage and, accordingly, they reported respiratory tract disease of multiple causes as pertussis.[16] This can be disproved, however, by looking at the sex ratio of cases during the time of the 1977 to 1979 outbreak in England and Wales and comparing it with earlier data from those countries. Pertussis is a unique disease in that clinical attack rates are generally higher in girls than in boys. In contrast, virtually all other respiratory tract infectious diseases of children—such as bronchiolitis and croup—have attack rates that are higher in boys than in girls. Figure 3 shows the male-female ratio of pertussis yearly attack rates in 0- to 9-year-old children in England and Wales. It is clear from this graph that this ratio did not change significantly during the 1977 to 1979 epidemic, and, therefore, the claim that there was misreporting of other respiratory tract illnesses as pertussis is unfounded.

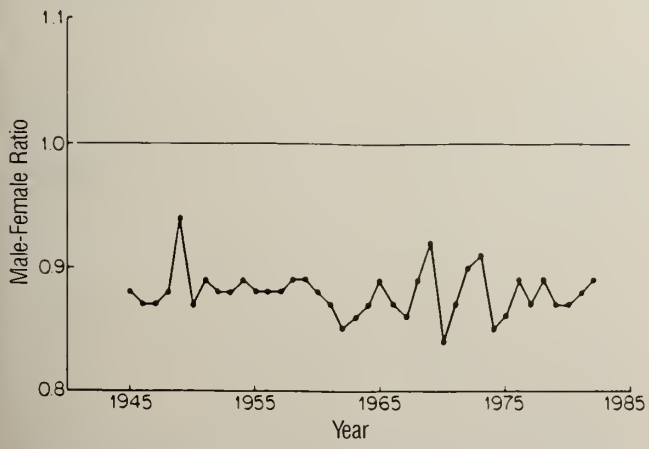

Figure 3.—The graph shows the male-female ratio of pertussis yearly attack rates in the 0- to 9-year-old age group in England and Wales (from Cherry[16[p16]]).

TABLE 1.—*The Distribution (Percentage) of Cases of Pertussis by Age Group in Different Time Periods in Massachusetts, England and Wales, and the United States**

		Age, Years				
		<1	1-4	5-9	10-14	≥15
Year(s)	Location	%				
1933-1939	Massachusetts	7.5	41.1	46.0	4.1	0.9
1945-1949	England and Wales	10.4	56.9	29.2	2.0	1.4
1970	England and Wales	12.1	43.6	38.9	3.5	1.8
1978-1981	United States	53.5	26.5	8.2	5.4	6.5
1984-1985	United States	42.5	23.0	8.4	6.3	16.5

*From Gordon and Hood,[2] Centers for Disease Control,[4,5] and Cherry.[16]

Mortality

In Figure 1, in which both mortality and morbidity rates in the United States are presented, it is clear that while morbidity was not falling before immunization, the mortality rate was. This decrease in mortality from pertussis is not surprising since death rates from all infectious respiratory tract illnesses have been falling throughout this century. However, when the rate of pertussis deaths in children younger than 1 year is examined—this being the age of major mortality with this disease—it is clear that the rate of decrease in mortality changed dramatically after the introduction and widespread use of pertussis immunization. As noted from the data of Mortimer and Jones, the fall in mortality changed from roughly 5-fold in the first 44 years of the century to close to 85-fold in the second 40 years.[23]

Surprisingly, in England and Wales the death rate did not increase during the 1977 to 1979 epidemic. In addition, the case-fatality rate in England and Wales is much below that in the US for comparable periods. Because it seemed unlikely that this difference could be explained by such things as better medical care, I investigated the possibility that the exceptionally low mortality rate was due to the misreporting of pertussis as deaths due to other infectious disease illnesses of the respiratory tract.[16] In this investigation it was noted that the death rate due to all respiratory tract infectious illnesses other than pertussis clearly increased during the 1977 to 1979 epidemic and started to increase again at the beginning of the 1982 to 1983 epidemic. Miller and associates and Nicholl and Gardener carried out similar projects, and both investigations noted a similar increase in reported deaths due to nonpertussis respiratory tract illness during the 1977 to 1979 pertussis epidemic.[24,25] My findings suggest that there were about ten pertussis deaths in infants reported as due to other causes for every death reported as due to pertussis. From these data, it appears that the pertussis case-fatality rate for infants in England and Wales was about 1.5%. During the same time period the infant case-fatality rate in the United States was about 1.0%.[3,5,6]

Morbidity

Pertussis morbidity data for 1984 and 1985 as compiled by the Centers for Disease Control are presented in Table 2. Overall, 41% of the patients were admitted to hospital, 12% had pneumonia, 1.7% had seizures, and 0.5% had encephalopathy. Morbidity was greatest during the first six months of life; in this age group, 74% were admitted to hospital, 20%

TABLE 2.—*Percentage of Pertussis Patients Admitted to Hospital and Percentage With Complications, by Selected Age Groups—United States, 1984 and 1985**

		Admitted to Hospital	Complication		
			Pneumonia†	Seizures	Encephalopathy
Selected Age Group	No.	No. (%)	No. (%)	No. (%)	No. (%)
<6 months	1,771	1,302 (73.5)	347 (19.6)	46 (2.6)	14 (0.8)
6-11 months	498	294 (59.0)	92 (18.5)	15 (3.0)	2 (0.4)
1-4 years	1,000	232 (23.2)	96 (9.6)	15 (1.5)	3 (0.3)
5-9 years	413	33 (8.0)	14 (3.4)	4 (1.0)	3 (0.7)
10-14 years	292	16 (5.5)	6 (2.1)	0 (0.0)	0 (0.0)
>14 years	745	43 (5.8)	18 (2.4)	1 (0.1)	0 (0.0)
All ages‡	4,728	1,921 (40.6)	574 (12.1)	81 (1.7)	22 (0.5)

*From Centers for Disease Control.[4(p169)]
†Confirmed by x-ray film.
‡Includes patients of all ages and 9 patients of unknown ages.

TABLE 3.—*Less Serious Events After 15,752 Diphtheria-Tetanus-Pertussis (DTP) and 784 Diphtheria-Tetanus (DT) Immunizations**

	DTP Group		DT Group		
Reaction	No.	(%)	No.	(%)	P Value
Local					
Redness	5,891	37.4	60	7.6	<.0001
Swelling	6,411	40.7	60	7.6	<.0001
Pain	8,018	50.9	78	9.9	<.0001
Systemic					
Fever (≥38°C)†	3,605	46.5	27	9.3	<.0001
Drowsiness	4,962	31.5	117	14.9	<.0001
Fretfulness	8,412	53.4	177	22.6	<.0001
Vomiting	977	6.2	20	2.6	<.0001
Anorexia	3,292	20.9	55	7.0	<.0001
Persistent crying	488	3.1	5	0.7	.0003
High-pitched, unusual cry	17	0.1	0	0.0	.3574

*Modified from Cody et al.[26(p652)]
†Fever was evaluated after 7,753 DTP and 292 DT immunizations. Children whose temperature was recorded at 3 and 6 hours after immunization are reported.

had pneumonia, 2.6% had seizures, and 0.8% had encephalopathy.

Pertussis Vaccine Reactions

The 1978-1979 UCLA Study

LARRY J. BARAFF, MD*: From January 1, 1978, to December 15, 1979, a prospective study of reactions occurring within 48 hours of diphtheria and tetanus toxoids and pertussis vaccine (DTP) administration was conducted by myself and other investigators at the UCLA School of Medicine, Kaiser Permanente Medical Group, and the Bureau of Biologics of the Food and Drug Administration.[26-28] The purpose of this study was to determine accurately the rates of both minor and more serious events associated with the use of DTP vaccines licensed in the United States. A control group received diphtheria and tetanus toxoids adsorbed vaccine (pediatric) (DT) to determine the difference in reaction rates between DTP and DT recipients and by implication the reactogenicity of the pertussis component of the vaccine. A total of 15,752 doses of DTP and 784 doses of DT immunizations were given to infants and children 0 to 6 years of age who were subsequently evaluated for reactions that occurred within 48 hours of immunization.

Less serious events. Table 3 presents the number and percent of vaccine recipients who manifested less serious reactions following DTP and DT immunization. Local reactions were reported following approximately 40% to 50% of DTP vaccinations. In contrast, the same reactions occurred after only 8% to 10% of DT immunizations ($P < .0001$). The frequencies of less serious systemic reactions following immunization were also significantly different in the DTP and DT groups. For example, fever (temperature >38°C) occurred following 46.5% of DTP immunizations and only 9.3% of DT immunizations. Only children whose parents recorded temperatures at least at three and six hours following immunization were included in these frequency calculations of febrile reactions because these were the times when fever was most likely to be present. Other less serious reactions, including drowsiness, fretfulness, vomiting, anorexia, and persistent crying were two to three times more frequent in the DTP group.

More serious events. Serious events occurred in 18 children within 48 hours of DTP immunization. These included nine convulsions and nine hypotonic-hyporesponsive episodes. Tables 4 and 5 present more detailed information regarding these reactions. The children who experienced convulsions ranged in age from 2 months to 5 years. Convulsions were noted following all four of the primary series immunizations. All occurred within 24 hours of immunization, with a median time of 14 hours. All but two children had elevated temperatures; two of those with fever had a previous history of febrile convulsions. Eight of nine children had complete neurologic examinations, all of which gave normal findings. Four children had electroencephalograms, all of which were normal.

Nine children experienced what were termed hypotonic-hyporesponsive episodes. This descriptive term applies to an unusual and characteristic reaction associated with DTP immunization. All such reactions occurred within ten hours of immunization and usually within four hours. Usually the infant or child was pale, hypotonic, and unresponsive to his or her parents for periods ranging from 10 minutes to 36 hours. These reactions were associated with the initial three doses of the primary immunization series. Seven children were noted to be febrile and three had a temperature of 40°C or higher. None of these children had a past medical history of neurologic problems, convulsions, or developmental delay. All returned to normal activity and were normal when evaluated by either their physicians or the investigators.

There were no episodes of encephalopathy, permanent neurologic damage, or death within the 48-hour follow-up

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period of this project. As stated, all children who experienced more serious reactions returned to a normal state within four days of immunization. The parents of 16 of these 18 children have been subsequently contacted after an interval of six to seven years, and all of the children were considered normal by their parents and were doing well in school.[29]

Neurologic Disease and Death Temporally Associated With Immunization

Neurologic Disease

DR CHERRY: The major controversy surrounding pertussis immunization today is related to the risk of so-called pertussis vaccine encephalopathy. The question that should be raised at this point is, Is there such a thing as pertussis vaccine encephalopathy?

From medical textbooks and immunization statements, such as those of the American Academy of Pediatrics and the Centers for Disease Control, it is clear that authorities have believed in the occurrence of pertussis vaccine encephalopathy.[30-32] At issue scientifically was not whether there was or was not a problem but what the incidence of the problem was.

In looking at the problem of neurologic disease relating to pertussis immunization, it is important to realize that there was a historic precedent to think that neurologic disease would occur. When pertussis immunization was instituted in the 1930s, there had been considerable previous experience with smallpox vaccine, rabies vaccine, and antisera of various descriptions.[33,34] A small number of persons who were immunized against smallpox had vaccine-induced encephalitis, and this illness was clearly inflammatory in nature. Similarly, persons who received rabies immunization frequently had inflammatory neurologic disease and antiserum therapy for the prevention of tetanus, and the treatment of other illnesses was frequently associated with inflammatory demyelinating neurologic problems.

In 1954, Miller and Stanton in a study of neurologic reactions following immunizations noted that neurologic disease also occurred in temporal association with pertussis vaccination, but it was unlike the other postvaccine and antiserum reactions.[34] Specifically, the illnesses that occurred in children following pertussis immunization were no different from the neurologic diseases that were occurring in unimmunized children of the same age. The illnesses that were occurring in vaccinated children were similar to the onset of severe convulsive disorders with mental retardation in children who were not vaccinated. Although this observation was made more than 30 years ago, it has generally been assumed in the medical literature that neurologic disease, when it occurred in temporal association with immunization, had a cause-and-effect relationship. It is obvious today that this assumption should be challenged. Without some epidemiologic or specific pathologic evidence of a cause-and-effect relationship, it is possible that no cases of temporally associated neurologic disease are due to pertussis immunization.[35]

The early literature on pertussis immunization contains scattered reports of postvaccination neurologic illness. In an early vaccine trial, Madsen reported on two neonates who convulsed and died immediately after immunization (Table

TABLE 4.—*Occurrence of Convulsions in 9 Children Within 48 Hours of DTP Immunization**

Age	Sex	Series No.	Time After Vaccination, hr	Maximum Temperature, °C	Duration of Seizure	EEG Findings	Neurologic Examination Findings	Comments
6 mo	♂	3	4+8	37.2	10-15 sec	NI	NI	2 brief episodes of opisthotonos
6 mo	♀	3	14	38.8	30-60 sec	NI	NI	3 major motor seizures within 10 min
2 mo	♀	1	5	37.5	60 sec	NI	NI	6 clonic seizures within 30 min with screaming
5 yr	♂	3	13	38.9	20-30 sec	NI	NI	4 tonic seizures within 30 min
3 yr	♂	1	15	39.4	2-3 min	NO	NO	1 major motor seizure; prior febrile convulsions; no medication
10 mo	♂	2	5	41.0	30 sec	NO	NI	1 major motor seizure; examination of CSF normal; subsequent roseola
19 mo	♀	4	7	"Fever"	3-5 min	NO	NI	1 major motor seizure; prior febrile convulsion; no medication
18 mo	♂	4	23	38.3	5 sec	NO	NI	1 episode of opisthotonos
18 mo	♂	4	14	39.4	3-5 sec	NO	NI	1 major motor seizure; examination of CSF normal

CSF=cerebrospinal fluid, DTP=diphtheria-tetanus-pertussis, EEG=electroencephalogram, NI=normal, NO=not obtained

*From Cody et al.[26(p654)]

TABLE 5.—*Occurrence of Hypotonic-Hyporesponsive Episodes (HHE) in 9 Children Within 48 Hours of Diphtheria-Tetanus-Pertussis Immunization**

Age, mo	Sex	Series No.	Time After Vaccination, hr	Maximum Temperature, °C	Duration of HHE	Comments
2	♀	1	3	39.2	3 hr	Pale, limp, and unresponsive; prior persistent crying
2	♀	1	10	38.6	15 hr	Unarousable and would not eat; irritable and lethargic thereafter, with shrill cry
7	♀	3	1	40.0	36 hr	Pale, listless, and hypotonic; private pediatrician's diagnosis, "encephalitis"
7	♀	2	1	38.9	17 hr	Lifeless, limp, pale, and would not suck
4	♀	2	4	Not obtained	10 min	Lifeless, limp, pale, unresponsive; hypoventilation and cyanosis
18	♀	2	10	40.0	20 min	Limp and unresponsive
2	♀	1	1	37.4	20 min	Pale, limp, unresponsive
3	♀	2	3	38.3	1 hr	Limp, lethargic, unresponsive
7	♀	3	1	40.5	7 hr	Flushed, limp, listless, and unresponsive

*From Cody et al.[26(p654)]

6).[36] Although the unique stories in these two cases suggest a cause-and-effect relationship, the limited quality control of the experimental vaccines of the time and the repeated dosing would suggest the possibility that the deaths were due to endotoxemia. In 1948 Byers and Moll reported a series of 15 cases seen at Boston Children's Hospital during the preceding ten years (Table 7).[37] The illnesses in most of these children were severe and encephalitic in nature and differed from the usual neurologic illness that today is attributed to pertussis immunization.

During the period from Madsen's first report until 1979, there were more than 1,000 individual case reports in the literature of serious neurologic illness in temporal association with pertussis immunization.[26] Until 1960, however, there had been no attempt to determine a rate of occurrence of postvaccine encephalopathy. In that year Ström published the results of a survey that he carried out in Sweden from 1954 to 1958[38] in which he found a rate of death, or permanent defect, of 1 per 17,000 children. These findings were, however, severely criticized by Malmgren and colleagues.[39] From Ström's data, they calculated a risk of permanent damage of 1 per 50,000 immunized children, rather than the 1 in 17,000 reported by Ström. In 1967 Ström published a second study covering the period 1959 to 1965, and in this he calculated a rate of destructive encephalopathy of 1 per 170,000 vaccinated children.[40] In 1979 Hannik and Cohen reported the results of a 12-year study in the Netherlands in which they noted a rate of encephalopathy of 1 per 400,000 vaccinated children.[41] In 1974 Prensky, using estimates of neurologic disease in the Boston area, concluded that post-pertussis immunization encephalopathy occurred at a rate of 1 case per 180,000 children.[42]

In all of those attempts to determine a rate of neurologic disease following pertussis immunization, there was no control for temporally related events due to other causes. The only way to obtain a true rate would be to do a study that was controlled for temporally related events due to other causes. To date, the results of three such studies have been published. In 1983 Pollock and Morris reported the results of a seven-year longitudinal prospective cohort study carried out in the North West Thames region of England.[43] Unfortunately, this study was hampered by the bias introduced because of the national publicity relating to pertussis vaccine reactions. During the study period, 134,700 children received three doses of DTP and 133,500 children received three doses of DT. There were 12 instances of neurologic disorders following DTP administration and 2 instances of neurologic disorder following giving DT. Four of the neurologic disorders following DTP administration occurred within four days of immunization, whereas none of the neurologic reactions following the administration of DT occurred within this time period. Of the four children with neurologic events after receiving DTP, one child was found to have a coxsackievirus B5 encephalitis and the three other children all had some evidence of an infectious illness at the time of the event. In their discussion, the authors concluded that there was no convincing evidence indicating a causal relationship between DTP vaccination and neurologic damage.

Another study, the National Childhood Encephalopathy Study (NCES), was carried out in England, Wales, and Scotland from July 1, 1976, to June 30, 1979.[24,44-46] This was a case-control study that included all children aged 2 to 35 months with serious acute neurologic disorders who were admitted to hospital. During the study period there were 1,182 children admitted with acute severe neurologic illness, and for each case, two controls were matched on the basis of sex, age, and geographic area. The results of this study have been extensively analyzed and presented in various forms in the medical literature. In one of the final analyses to date, which included only previously well children, excluded infantile spasms, and there was an end result of death or neurologic impairment after 12 months, the relative risk of DTP immunization was found to be 4.7 and the attributable risk was 1:330,000 (95% confidence interval, 1:18 million to 1:50,000).[24] In one paper on this study, infantile spasms were analyzed separately and no significant association was found between pertussis immunization and the illness.[46] Although the NCES is clearly the best study to date on rare events and pertussis immunization, there are some, including myself, who think that the results do not necessarily show a cause-and-effect relationship of the vaccine to neurologic illness but more likely suggest a moving forward in time or the calling attention to a neurologic event that was going to happen or was in the process at the time. Most recently it has been found in the process of a landmark legal trial in the United Kingdom that NCES study biases led to an overstatement of risk.[47]

In 1977 Melchior published the results of his study on the relationship of DTP immunization and infantile spasms in Denmark.[48] This study was made possible by the fact that in Denmark immunizations were carried out differently in two time periods. In the first time period before 1970, pertussis immunization was carried out at ages 5, 6, and 15 months, whereas in the second time period from 1970 to 1975, it was carried out at ages 5 weeks, 9 weeks, and 10 months. It was found that 42% of the cases of infantile spasms in each time period occurred before age 5 months. If pertussis immunization had any major causative effect for infantile spasms, it would be expected that a greater percentage of the cases

TABLE 6.—*Report in 1933 of 2 Deaths Shortly After Pertussis Immunization**

Case 1

Immediately after birth, 0.1 ml (1 billion bacilli) vaccine given; no symptoms

4 days later, 0.15 ml vaccine given; ½ hour later, contractions of arms and legs occurred, followed by cyanosis, hiccup, convulsions, and death within a few minutes

Case 2

A 2,250-gram baby, at 8th day of life, was given 0.1 ml vaccine; no symptoms

3 days later, 0.2 ml vaccine was given; 2 hours later child died suddenly with slight cyanosis

At postmortem examination, no definite cause of death could be established

*From Madsen.[36]

TABLE 7.—*Report of 15 Children With Neurologic Illness After Pertussis Immunization in 1948**

15 children with post-pertussis vaccination neurologic illness admitted to hospital during 10-year period, ages 5 to 18 mo; mean 9 mo

Vaccine doses 2 to 4 times present-day vaccines in 11 of 15 children

Cerebrospinal fluid of 6 of 8 children abnormal

Acute illnesses all severe

*From Byers and Moll.[37]

would have occurred early in the second time period because of the earlier immunization.

Deaths

Since the first deaths in 1933 noted by Madsen, there have been other scattered reports of deaths that were attributed to pertussis immunization.[34] Two categories of deaths must be considered in the analysis of a possible relationship to pertussis immunization. The first category includes children who have a symptomatic illness before dying and some of these symptoms are those of known pertussis vaccine reactions. The second category is the sudden infant death syndrome (SIDS) in which there is no or minimal antecedent illness and no significant pathologic findings noted at postmortem examination.

Over the past 50 years, there have been scattered reports of non-sudden infant death syndrome deaths following pertussis immunization. However, few of these have had adequate studies to rule out other causes and in only one instance has some form of control data been available. In the only controlled study, which was the North West Thames region study, there were two non-SIDS deaths following DTP immunization and none following DT immunization.[43] Of these two children, one died of pneumonia 48 hours after vaccination and the second child died of Reye's syndrome 8 days after the procedure. Although it is possible that some deaths have been anaphylactic in origin, there is little evidence at this time to support an association between pertussis immunization and non-SIDS temporally related events.

The association of pertussis immunization and SIDS has received much attention in the lay media recently. In contrast to non-SIDS temporally related deaths, there have been several controlled studies that have looked at the association of pertussis vaccine with SIDS.[49-52(p131)] During a study period of January 1, 1979, to August 23, 1980, Baraff and coworkers noted a statistically significant number of excess deaths in the week following immunization (observed 17, expected 6.75; $P = .0005$), and the greatest number of deaths occurred within 24 hours of immunization (observed 6, expected 0.96; $P = .0005$).[49] This study was hampered by the fact that only 38% of the parents of infants with SIDS were surveyed. In addition, the study was criticized by Mortimer and colleagues because there was considerable potential for recall and observer bias and, most important, the expected frequency rate that was used did not take into consideration the well-known age distribution of SIDS.[53]

In 1982 Taylor and Emery carried out a retrospective case-control study in Sheffield, England, in which they were unable to show an association between DTP immunization and death.[51] Recently the results of a large National Institutes of Child Health and Human Development case-control study involving 800 SIDS victims were published.[50] In this study, no correlation between DTP immunization and the occurrence of the sudden infant death syndrome was found. Finally, an extensive study in Norway failed to find an association between pertussis immunization and the occurrence of SIDS.[52]

Old and New Vaccines and the Future Control of Pertussis

ERIK HEWLETT, MD*: There are two major issues that must be addressed in considering a new component pertussis vaccine: What bacterial components should be included? and How should the vaccine be used? I shall begin by giving a brief review of the history of pertussis vaccine development and a perspective on what is to come in the next few years.

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TABLE 8.—*Pathophysiologic Sequence of Events in Pertussis and Candidate Virulence Factors for Mediating Each Phase of the Disease**

Attachment	Filamentous hemagglutinin
	Pertussis toxin
	Agglutinogens
Invasion or disruption of host defenses	Adenylate cyclase toxin
	Tracheal cytotoxin
	Pertussis toxin
Local tissue damage	Tracheal cytotoxin
	Adenylate cyclase toxin†
	Dermonecrotic toxin†
	Hemolysin†
Systemic pathology	Pertussis toxin

*From Weiss and Hewlett.[58]
†These are logical candidates, but there are little or no supporting data.

The first step in this process was the identification and isolation of *B pertussis* in 1906 by Bordet and Gengou.[13] In a remarkably short time, several scientists attempted to prepare a vaccine from killed *B pertussis* organisms and were successful.[36,54] Recognizing the need for an animal model to evaluate these vaccines, Kendrick and associates developed the mouse intracerebral challenge test,[55] which was validated as a correlate of human protective activity in the British Medical Research Council trials[56] and is used to this day for quantitating vaccine potency. These early successes probably delayed the subsequent evolution of the vaccine.

The introduction of whole-cell pertussis vaccine into widespread use in the 1950s clearly had a major influence on the incidence and severity of clinical pertussis in our population.[16,23] Although there has been some debate about this issue because of a report that suggested that the incidence of pertussis in England and Wales was declining before mass immunization,[14] the recurrence of pertussis in nations such as England and Japan, in conjunction with reduced vaccine use, has established the role of vaccine in the control of the disease. From nearly the beginning of pertussis vaccine use, there were reports of adverse neurologic events temporally associated with vaccine administration.[37,57] The vaccine reactions, such as those described earlier by Drs Baraff and Cherry, have served as a major stimulus for the development of a pertussis vaccine containing the specific bacterial components important for protection and eliminating those that are unnecessary.

One approach in considering which parts of the bacterium should be included in such a non-whole-cell vaccine is to review the pathophysiology of pertussis and consider the relative importance of recognized virulence factors. This has been the subject of several recent reviews and is beyond the scope of this presentation.[58-61] A summary of the compiled conclusions is given in Table 8.

The sequence of events that is common to many infectious diseases begins with the introduction of the pathogen into the host and attachment of that pathogen to specific tissues. During the entire process, there is invasion or disruption (or both) of both specific and nonspecific host defense mechanisms, a requirement for a virulent pathogen. There is often local damage characteristic of the particular

infecting organism and, in many cases, dissemination of the organism or its products, resulting in systemic manifestations of disease. In the case of pertussis, accumulated data suggest that not only is filamentous hemagglutinin involved in the attachment of the *Bordetella* organism to ciliated cells of the respiratory tract, but pertussis toxin and some of the agglutinogens (as components of the surface fimbriae) may also contribute.[61,62]

Three components of *B pertussis*—adenylate cyclase toxin, pertussis toxin, and tracheal cytotoxin—have the capacity to disrupt host immune-effector cell function and clearance mechanisms in model systems. It has been hypothesized that tracheal cytotoxin,[61] as well as dermonecrotic toxin, adenylate cyclase toxin, and hemolysin, may play a role in establishing the local lesion induced by *B pertussis* in the respiratory tract.[58,59,61] Pertussis toxin is the only one of these components that produces systemic effects in experimental animals—that is, lymphocytosis—that have analogous laboratory findings in patients with clinical pertussis. For this reason, pertussis toxin has been designated by some investigators as the leading candidate for mediating the systemic manifestations of the disease.[63] This designation is misleading because the only systemic manifestation of pertussis is lymphocytosis. It is important to note, however, that pertussis toxin alone is not responsible for the disease process—that is, pertussis is not a single-toxin disease in the way that tetanus is. This is best shown by the study of Toyota and co-workers, who injected purified pertussis toxin into normal adult volunteers at doses of 0.5 and 1.0 μg per kg without the development of significant adverse effects or of any of the manifestations of clinical pertussis.[64]

Using these data from various studies in animals and humans, it appears that there are numerous *B pertussis* virulence factors and that an immune response to neutralize the activities of each could potentially contribute to protection against infection, disease, or both. Recognizing this potential problem, however, Manclark has proposed criteria for selecting antigens for inclusion in a component pertussis vaccine.[65] These criteria include the availability of the component in sufficient quantities for use in a vaccine, the availability of an assay procedure for evaluating and quantitating the component, and laboratory evidence that the component can function safely and effectively as a protective antigen. These specific requirements illustrate the problems associated with the trial-and-error process by which a number of investigators attempted to extract "protective antigen" from whole-pertussis organisms for inclusion in a non-whole-cell vaccine.[66-68] The only end point was a preparation that would pass the mouse potency test without a determination of the extracted components involved. It was the observations of Sato and co-workers,[69] showing that there is a sufficient quantity of pertussis toxin and filamentous hemagglutinin in the culture medium of *B pertussis* for purification and that those two components so prepared protected mice against both intracerebral and aerosol challenges, that served as the basis for the component vaccines being used currently in Japan. Additional data will be required to determine whether others of the components described above can be prepared in such a way as to fulfill the requirements proposed by Manclark.

Because inactivated pertussis toxin at a sufficient concentration has been shown to be fully protective in the mouse potency test, it has been proposed that it might be the only component required in a recent efficacy field trial in Sweden in which the use of pertussis toxoid alone and that of pertussis toxoid plus filamentous hemagglutinin were compared with placebo.[71] Although both vaccines were found to be efficacious, the percent efficacy was disappointing when compared with available data regarding presently licensed whole-cell vaccines.[72] In addition, protection did not correlate with antibody levels against pertussis toxin.[73]

TABLE 9.—*Relation Between Interval Since Last Dose of Pertussis Vaccine and Attack Rate in the Setting of a Community Outbreak**

Years Since Last Pertussis Vaccine	Attack Rate (Percentage of Exposed)
0-3	21
4-7	47
8-11	65
≥12	95

*From Lambert.[11]

Additional recent developments that will influence the evolution of component vaccines are the isolation and cloning of the genes for pertussis toxin[74,75] and filamentous hemagglutinin.[76] The availability of these data will allow the generation and expression of large quantities of biologically inactive pertussis toxin, or its subunits, which can be used with filamentous hemagglutinin and agglutinogens in a component vaccine. Thus, it is clear that the initial formulation (first generation) of component pertussis vaccine will be replaced in the future by further refined preparations that may contain additional components.

These exciting developments provide a new perspective on the second question I want to address, namely, How should pertussis vaccine be used in our population to control pertussis? With the current immunization schedule, in which children are give DTP vaccine at 2, 4, 6, and 15 months of age with a final booster at age 4 to 6 years and no further doses thereafter, the majority of the population is left without protection. This point is best illustrated by the data from Lambert in his description of a pertussis outbreak in Kent County, Michigan.[11] There was a direct correlation between the attack rate among immunized persons and the duration since last dose of vaccine (Table 9). These data show that the protection elicited by whole-cell vaccine decreases with time, resulting in an attack rate of more than 95% for persons 12 or more years beyond their last dose of vaccine. This means that in a population such as that of the United States, where vaccine acceptance rates probably exceed 90% and there are few cases in children, there are a large number of susceptible persons (older than 16 to 18 years).

Clinical pertussis is well documented in adults,[19,77-79] and in fact it has been described as "grandmother's cough" in reference to the role of a portion of the adult population in spreading the infection to susceptible children. By far the majority of cases identified in adults are, however, recognized only in the setting wherein a susceptible child is the index case. The diagnosis is not one that is frequently entertained when an internist sees a patient with cough of more than a week's duration.

An anecdote from our recent experience illustrates this problem. Five adults with an interest in auto racing traveled from Virginia to Indiana for the Indianapolis 500 in May 1986. They ranged in age from 25 to 65 years and were in

generally good health. Because of a series of rain delays of the race, the group was together indoors for most of the trip, and during that time one person had rhinorrhea and a cough develop that became paroxysmal. Seven to ten days after returning home, the other four persons had the onset of rhinorrhea, watery eyes, and dry cough without fever, which progressed to paroxysmal cough lasting several months. One (25 years of age), who had been fully immunized against pertussis as a child, had cough syncope develop, which persisted for several months. Each of these patients was treated with antibiotics (erythromycin and others) by their physicians for bronchitis during the course of the illness, but without response. Although one patient wondered whether she might have "whooping cough," that diagnosis was not considered by the physicians involved. None of the patients were culture-positive at 2½ months into their illness, but all five had high titers of antipertussis toxin or antifilamentous hemagglutinin antibodies, or both, as determined by the enzyme-linked immunosorbent assay (carried out by Burstyn and co-workers,[80] Center for Drugs and Biologics, Food and Drug Administration). Several children were exposed to these adults during the course of their disease, but all were fully immunized and pertussis did not develop in any of them.

This anecdote shows what is likely to be occurring in a significant number of adults in our population, that is, the development of unrecognized clinical pertussis. The disease is well documented to be atypical in adults relative to classic whooping cough in infants and small children[19,77-79] and thus is infrequently diagnosed. Symptoms can range from a transient cough to prolonged cough diagnosed as bronchitis to the full clinical illness seen in children: paroxysmal cough with gasping for breath and vomiting after the paroxysm. It is this population of infected persons that serves as the source for many of the isolated "sporadic cases" occurring in susceptible children.[21,22] For this reason, a continued use of the current whole-cell vaccine in children is essential until a new preparation is licensed.[81]

Although the current whole-cell vaccine has been used to immunize adults—nurses, physicians, and others with patient contact—in hospitals during epidemics involving nosocomial transmission,[18-20] it will never be routinely used in the general adult population because of its alleged reactogenicity. The development of component pertussis vaccines, however, provides a novel opportunity for making a change in immunization practices. Incorporating a component pertussis vaccine into adult tetanus and diphtheria toxoid for routine administration every ten years, as is the current recommendation for tetanus and diphtheria toxoid, could increase immunity in adults, reduce the prevalence of transmission in the adult population, and ultimately result in control or, in theory, eradication of pertussis in our population.

At present, at least three trials with four different acellular pertussis vaccines have been carried out in adults.[69,82] In Sweden, 47 adults were immunized with a licensed Japanese vaccine containing both pertussis toxin and filamentous hemagglutinin antigens.[83] The vaccine induced a good antibody response to both antigens. Most vaccinees had mild local reactions following immunization, and two subjects reported systemic symptoms. In France, 164 adults have been immunized with two different experimental acellular vaccines with only mild resulting signs and symptoms.[82] In the United States, Sekura and associates have immunized 146 adults with a toxoid vaccine and noted only mild local reactions.[70]

In summary, new component pertussis vaccines have been developed and are being tested for immunogenicity (in the US and other countries) and for efficacy against infection with *B pertussis* (in Sweden and Japan). While these vaccines appear to have fewer associated local and mild systemic reactions, the data are not yet available on a possible association with severe neurologic dysfunctions. Developmental efforts continue, based in part on current and previous studies of the pathophysiology of pertussis and the role of various virulence factors of the organism, and new discoveries are likely to be reflected in second- and third-generation component pertussis vaccines. With the recognition of cases of diphtheria in the adult population[84] and in the context of increased efforts to achieve adult immunization against preventable diseases such as tetanus, diphtheria, and influenza, it is now clear that pertussis is also an issue. The recognition of the occurrence of pertussis in adults as a cause of morbidity and a source of infection for infants has placed renewed importance on the possible use of a new component pertussis vaccine in that population. With complete immunization coverage of all age groups, pertussis is a potentially eradicable disease.

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Medical Staff Conference

Wegener's Granulomatosis

Discussant
KENNETH E. SACK, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *The prompt diagnosis of Wegener's granulomatosis has been made all the more important because of the availability of highly successful chemotherapy for what was formerly a uniformly lethal disease. The therapy, however, can itself cause pulmonary complications that may be confused with a recurrence of the disease. These issues were recently illustrated by a patient seen in our institution. The case will be both presented and discussed by Kenneth Sack, MD, Director of the Clinical Programs in Rheumatology.*

KENNETH E. SACK, MD†: The patient is a 57-year-old Palestinian woman who, in September 1980, presented with fever, episcleritis, nasal congestion, distal sensory neuropathy, and cavitary pulmonary infiltrates. Sinus films and the results of renal function tests were normal, but a urinalysis showed hematuria and red blood cell casts. The specimen of a transbronchial biopsy done at another hospital showed only plasma cell infiltrates, but an open-lung biopsy specimen showed vasculitis and necrotizing granuloma formation (Figure 1). Culture of the specimen yielded *Mycobacterium gordonae,* which was not considered pathogenic. Her purified-protein-derivative skin test, however, was positive, and although Wegener's granulomatosis seemed likely, she received a course of isoniazid, ethambutol hydrochloride, rifampin, and streptomycin without clinical improvement. Her serum creatinine level subsequently rose to 353.6 μmol per liter (4.0 mg per dl), supporting the impression of Wegener's granulomatosis. Treatment with prednisone and cyclophosphamide produced a resolution of symptoms, a notable clearing of the chest infiltrates, and a return of normal renal function. Her medication therapy was discontinued after 14 months.

After stopping immunosuppressive therapy, she had infrequent episodes of bacterial sinusitis that responded to antibiotic therapy. In January 1986 she presented with fatigue, sinusitis, episcleritis, hematuria, and new pulmonary nodules. A regimen of prednisone, 20 mg twice a day, and cyclophosphamide, 150 mg a day, was begun for presumed recurrent Wegener's granulomatosis. Her symptoms abated, but attempts to taper the immunosuppressive therapy resulted in their return. A chest x-ray film showed only minimal improvement.

In November 1986 she noted worsening shortness of breath. Pulmonary function tests showed a mild restrictive pattern with a normal diffusing capacity for carbon monoxide. The occurrence of fever in July 1987 prompted admission to UCSF. The chest radiograph now showed a diffuse interstitial pattern (Figure 2). The partial oxygen pressure was 72 torr with the patient breathing room air. A workup for an infectious process showed no abnormalities. Bronchoscopy and a transbronchial biopsy specimen showed interstitial inflammation, fibrosis, and organizing alveolitis, consistent with cyclophosphamide toxicity (Figure 3). Cyclophosphamide therapy was discontinued and a course of indomethacin begun.

A month later, she was readmitted with recurrent fever. A gallium scan showed increased uptake in both lungs, and she underwent an open-lung biopsy. The histologic appearance was again consistent with cyclophosphamide toxicity. The prednisone dosage was increased to 40 mg a day, and the patient's condition gradually improved after discharge.

Discussion

Wegener's granulomatosis is only one of many diseases producing the syndrome of vasculitis (Table 1).[1] Friedrich Wegener was the first to recognize this distinct form of vas-

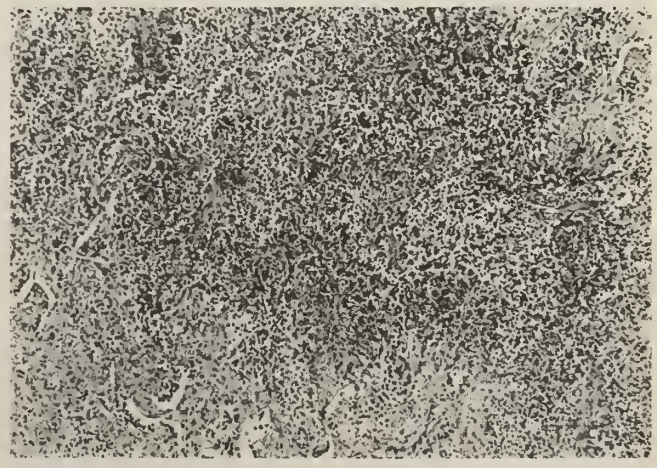

Figure 1.—The specimen of an open-lung biopsy shows necrotizing granulomas (original magnification × 100).

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(Sack KE: Wegener's granulomatosis [Medical Staff Conference]. West J Med 1989 Mar; 150:329-333)

culitis. In 1936, he reported on three patients in whom destructive lesions in the upper airways and disseminated vasculitis led to death within 6 to 14 months.[2] More than 20 years later, Walton reviewed 56 cases and confirmed the dismal outlook for patients with Wegener's granulomatosis[3]; Carrington and Liebow later noted that the disorder may also exist in a more benign "limited form."[4]

In this presentation I shall focus on the diverse clinical manifestations of this disease and the challenges of its treatment.

Clinical Manifestations

Wegener's granulomatosis begins most commonly as a hemorrhagic, destructive process involving the upper respiratory tract.[5] Early symptoms may include not only nasal discharge or obstruction as in the patient discussed here but also epistaxis, sinus pain, earache, tinnitus, vertigo, hearing loss, sore throat, and hoarseness (Table 2).[6-8] The nasal septum may eventually collapse, resulting in a saddle-nose deformity. Pulmonary involvement may manifest as dyspnea, cough, hemoptysis, and pleuritic pain.[6]

Renal involvement is a major cause of mortality in this disorder.[9,10] As in this patient, it may be initially asymptomatic, causing a delay in diagnosis or a failure to treat the underlying disease aggressively. In some cases progressive renal failure is the predominant clinical feature and, rarely, renal disease actually precedes the onset of pulmonary disease by many years.[11]

Almost every ocular structure is a possible target.[12] Vasculitis may affect the conjunctivae, sclerae, cornea, uveal tract, retina, and optic nerve. In addition, extension of sinus granulomas can obstruct the nasal lacrimal duct or cause ocular muscle dysfunction or proptosis.

Approximately two thirds of patients with Wegener's granulomatosis have musculoskeletal complaints,[13] ranging

Figure 2.—A chest radiograph shows bilateral, coarse, reticular interstitial markings and small nodular densities at the right lung base.

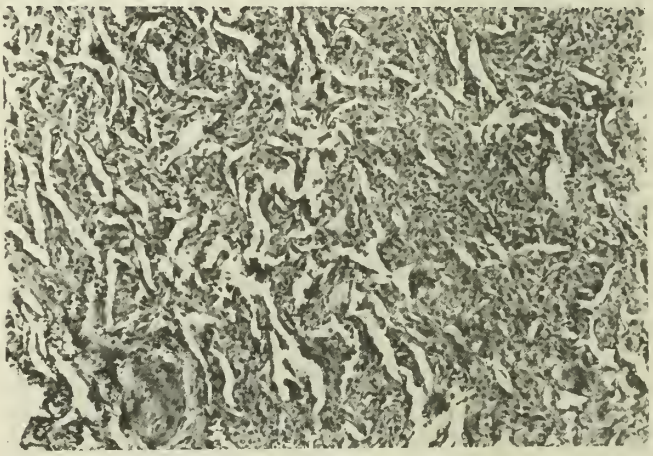

Figure 3.—A specimen of an open-lung biopsy shows interstitial inflammation and organizing alveolitis (original magnification × 100).

TABLE 1.—*Classification of the Vasculitides**

Form of Vasculitis	*Types*	*Vessels Involved*	*Pathology*
Systemic necrotizing vasculitis	Classic polyarteritis nodosa Allergic angiitis Granulomatosis (Churg-Strauss syndrome)	Small and medium-sized arteries	Necrotizing vasculitis (extravascular granulomas can occur with Churg-Strauss syndrome)
"Hypersensitivity" vasculitis	Schönlein-Henoch purpura Serum sickness Drug related Infectious Neoplastic Connective tissue disease Cryoglobulinemia Complement deficiencies Erythema elevatum diutinum Miscellaneous	Venules, arterioles, capillaries	Leukocytoclastic angiitis
Granulomatous vasculitis	Wegener's granulomatosis Lymphomatoid granulomatosis	Small and medium arteries	Necrotizing granulomatous angiitis (Wegener's); angiocentric lymphocytic infiltrates (lymphomatoid)
Giant cell arteritis	Temporal arteritis Takayasu's arteritis	Medium and large arteries	Giant cell arteritis
Miscellaneous	Mucocutaneous lymph node syndrome (Kawasaki's disease) Behçet's syndrome Thromboangiitis obliterans (Buerger's disease)		

*Modified from Fauci.[1]

from arthralgias and myalgias to nonerosive polyarticular arthritis. Sacroiliitis, auricular chondritis, and erosive arthritis are less common rheumatic manifestations.[14] The skin is rarely involved initially, but almost 50% of patients eventually have cutaneous manifestations. These may be petechial, purpuric, or nodular lesions that in some cases ulcerate or vesiculate.[15] In about 20% to 25% of cases, the disease affects the nervous system, either by vasculitis only or by contiguous granulomatous involvement. Neurologic findings are those of mononeuritis multiplex, cranial neuropathy, or diffuse cerebritis.[16,17]

TABLE 2.—*Organ Involvement in Wegener's Granulomatosis*

Organ	*Frequency, %*
Lung	95+
Paranasal sinuses	90+
Kidneys	80-85*
Nasopharynx	65-90
Joints	55-65
Skin	45
Ear	40-60
Eye	40-60
Nervous system	20-25
Heart	10-30
Larynx	10-20

Unusual Presentations

Breast mass
Erosive polyarthritis
Subglottal stenosis
Diffuse pulmonary hemorrhage and rapidly progressive renal failure
Headache and cranial neuropathy

*There may be renal involvement in 40% of cases in "limited" Wegener's granulomatosis.

TABLE 3.—*Differential Diagnosis of Upper Airway Involvement With Wegener's Granulomatosis*

Fungal infections	Histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, sporotrichosis, rhinosporidiosis
Bacterial infections	Glanders *(Pseudomonas mallei)*, listeriosis, rhinoscleroma *(Klebsiella rhinoscleromatis)*, leprosy, tuberculosis, syphilis
Granulomatous disease	Sarcoidosis
Neoplasia	Primary nasal tumors, plasmacytoma, lymphoma, midline reticulosis
Miscellaneous	Sinus histiocytosis with massive lymphadenopathy Granuloma secondary to intravenous drug abuse

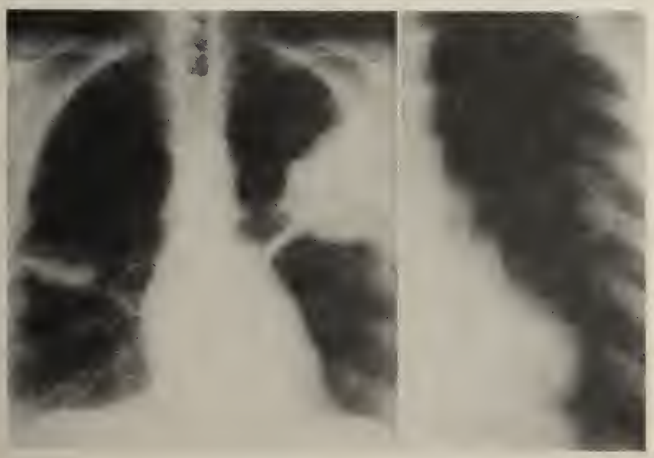

Figure 4.—Left, A chest radiograph of a patient with Wegener's granulomatosis shows 2 large peripheral infiltrates with irregular margins. **Right,** A lung tomogram shows a solitary cavitated lesion with an irregular thick wall (from Dieppe et al[25]).

Heart involvement is not usually a dominant feature in these patients, but reported cardiac complications include coronary arteritis, pericarditis, or myocarditis.[18] Supraventricular tachyarrhythmias are common. Heart block is rare.

In Table 2 I have included several unusual manifestations of the disorder.

Diagnosis

The early diagnosis of Wegener's granulomatosis has its pitfalls. A number of infectious, granulomatous, vasculitic, and neoplastic disorders of the upper respiratory tract present in much the same manner as this disease (Table 3). In addition, a biopsy specimen from tissues involved with this disorder frequently yields confusing histopathologic findings. There may be only fibrinoid degeneration with granuloma formation; the presence of giant cells is variable. Equally unpredictable is the degree of vascular and extravascular involvement. The predominance of extravascular lesions, occasionally in the absence of obvious vasculitis, has led some investigators to think that the primary lesion is a necrotizing granuloma and that vascular and extravascular tissues are closely related targets.[19]

Characteristic pathologic changes of Wegener's granulomatosis are often absent from biopsy specimens of the upper airway, but lung tissue, particularly when obtained from an open-lung biopsy, usually contains diagnostic granulomata and vasculitis.[6] Renal biopsy specimens show changes ranging from the more typical focal segmental glomerulonephritis to a necrotizing proliferative glomerulonephritis with crescent formation.[5,11] IgG and complement deposition occurs occasionally, often in a subepithelial location.

Nonspecific abnormalities occurring in patients with this disorder include anemia, thrombocytosis, an elevated erythrocyte sedimentation rate, abnormal urine sediment, hypergammaglobulinemia (particularly immunoglobulin [Ig] A and IgM), a positive rheumatoid factor, and serum immune complexes.[6] Many patients have an IgG antibody that binds to an as-yet-uncharacterized neutrophil cytoplasmic antigen.[20-23] Titers appear to correlate with disease activity, but the sensitivity and specificity of this antibody for the presence of Wegener's granulomatosis remain to be determined.

Sinus radiography frequently shows air-space opacification or membrane thickening. Although Wegener's granulomatosis can cause soft tissue destruction and occasional erosion through the walls of the sinuses, perforation of the hard palate or erosion through facial skin suggests a more aggressive neoplastic disease.[6]

Chest radiographic abnormalities occur in more than 50% of patients (Figure 4).[3,5,24,25] They include multiple pulmonary infiltrates or nodules, cavitary lesions (thick or thin-walled), consolidation, and hilar adenopathy. Tests of pulmonary function often show reduced lung volumes and decreased diffusing capacity. Also common is evidence of air-flow obstruction, usually indicating focal large airway disease.[26]

Etiology

The cause of Wegener's granulomatosis is unknown. The propensity for this illness to involve the airways provokes speculation that an inhaled antigen is the trigger. Searches for offending agents have been unrewarding, but as will be discussed later, recent successes using the combination of trimethoprim and sulfamethoxazole to induce remission point toward an infectious cause. It seems unlikely that *M gordonae* was responsible for this patient's illness because her disease progressed despite antituberculous treatment. Moreover, the well-circumscribed discrete granulomas typical of tuberculosis or sarcoidosis do not occur in Wegener's granulomatosis.

Involved tissues of patients with this disease seldom yield evidence of immune-complex deposition, but this does not completely exonerate immune complexes as initiators of the disease process. Finally, Elkon and co-workers report that these patients show an increased frequency of HLA-DR2,[27] a tissue type prevalent in patients with several other granulomatous disorders. This suggests a genetic predisposition for this type of inflammatory response.

Treatment

Although the use of steroids may provide a marginal benefit for these patients,[28] treatment with cytotoxic agents has dramatically improved survival.[5,6] In 1954 Fahey and associates reported that nitrogen mustard treatment transiently decreased sinus pain in a patient with Wegener's granulomatosis.[29] Not until the 1960s, however, were alkylators shown to be effective in treating this disease.[28-32] Then in 1974 Wolff and colleagues reported the outcome of 21 patients treated with cyclophosphamide over a 12-year period.[33] At the time of that report, 11 of the 17 patients with generalized disease and all of the 4 patients with limited disease were in remission. Compared with the dismal five-month survival reported by Walton,[3] this was a monumental improvement.

In 1983 Fauci and co-workers described the prospective experience of the National Institutes of Health in treating 85 patients with this disease over a 21-year period.[6] The protocol consisted of initiating treatment with cyclophosphamide, 2 mg per kg body weight per day orally, along with prednisone, 1 mg per kg per day orally. After two to four weeks, the prednisone dosage was gradually tapered and prednisone therapy eventually discontinued. The cyclophosphamide dosage was adjusted so that the leukocyte count never dropped below 3 to 3.4×10^9 per liter (3,000 to 3,400 per μl). After a year of clinical remission, the daily dose of cyclophosphamide was decreased by 25 mg every two to three months and the therapy was either discontinued or the drug maintained at a dose shown to prevent a flare-up of disease. A few patients with rapidly progressive disease began therapy with 4 to 5 mg per kg per day of cyclophosphamide and 2 mg per kg per day of prednisone or a soluble parenteral equivalent. Complete remission occurred in 79 of 85 (93%) patients, but the mean duration of therapy in these patients was 46 months. By contrast, 10 of 11 patients who received azathioprine as the initial therapy failed to obtain remission and required the initiation of cyclophosphamide. Current experience clearly favors using cyclophosphamide in the initial treatment of Wegener's granulomatosis, although azathioprine may successfully maintain a remission in patients unable to continue using cyclophosphamide.

The mechanism by which cyclophosphamide ameliorates disease activity in these patients is unclear. Cyclophosphamide is a cyclic mustard that is activated in the liver and that disrupts DNA synthesis.[34] B lymphocytes are sensitive to the effects of cyclophosphamide, but low doses of cyclophosphamide also can inhibit the function of T-suppressor lymphocytes; in higher doses it can suppress T-helper lymphocyte function.[35] Histopathologic study of the pulmonary vascular infiltrates by the immunoperoxidase technique shows a predominance of T lymphocytes and monocytes, with little evidence for immunoglobulin or complement deposition.[36] If, as these data suggest, cellular immune mechanisms are important in mediating the damage caused by this disease, cyclophosphamide could modify disease activity through its effects on this part of the immune system.

Recent reports indicate clinical remissions in patients with this disorder following the use of trimethoprim-sulfamethoxazole.[37,38] Why this antibiotic combination should be beneficial is unclear, but possible mechanisms include the eradication of an offending microorganism or the induction of immunosuppression by interfering with folate metabolism. Investigators at the Mayo Clinic continue to be enthusiastic about the use of this regimen for patients with this disease (R. DeRemee, MD, oral communication, July 1988), but knowing where trimethoprim-sulfamethoxazole fits in the therapeutic armamentarium requires further study.

A relapse in disease activity is often signaled by malaise, arthralgia, fever, new skin lesions, and an elevated erythrocyte sedimentation rate (or C-reactive protein). Clinicians should be aware, however, that damaged upper airway mucous membranes are more susceptible to bacterial invasion. Therefore, increased sinus pain or nasal drainage in a patient with otherwise quiescent disease frequently results from secondary infection, usually with *Staphylococcus aureus,* and requires appropriate treatment.[6]

Complications of Therapy

The complications of steroid therapy are well known, and they will not be reviewed. The use of cyclophosphamide has potentially serious side effects. Among these are marrow suppression, cystitis, gonadal dysfunction, interstitial lung disease, and the induction of neoplasia.[33]

To avoid bone marrow suppression, leukocyte counts should be monitored every two weeks and the dosage of cyclophosphamide decreased if the count approaches 4×10^9 per liter. Delaying dose adjustments until the leukocyte count is below this level invites disaster because profound marrow depression may have already taken place. Cyclophosphamide therapy can maintain a clinical remission without substantial reductions in the leukocyte count. Furthermore, Wolff and associates have shown that when the leukocyte count approaches 2×10^9 per liter (2,000 per μl), a catastrophic fall in the neutrophil count may ensue.[33]

Hemorrhagic cystitis, a serious complication of cyclophosphamide use is due to the toxic effects of the metabolite acrolein on the bladder wall. It may manifest as hematuria in the absence of apparent renal disease. Cystoscopy provides critical information regarding the condition of the bladder wall. Fauci and colleagues have been able to continue, without serious sequelae, maintenance cyclophosphamide therapy in several patients with mild drug-induced cystitis.[6] Adequate hydration minimizes the toxic effects of cyclophosphamide on the bladder wall.

Gonadal dysfunction, possibly irreversible, is another

common side effect of using cyclophosphamide. Women over the age of 30 are particularly susceptible to this complication, and some investigators suggest using oral contraceptives during immunosuppressive therapy to protect ovarian function.[39]

Cyclophosphamide therapy appears capable of inducing chromosomal damage to an even greater extent than chlorambucil, another alkylating agent.[40] Using cyclophosphamide, therefore, could induce a neoplasm. Although the degree of risk is not known, in only 1 of 85 patients observed over 21 years at the National Institutes of Health did a neoplasm develop; that patient had a lymphoma.[6] In view of the high lethality of Wegener's granulomatosis, the risk of neoplastic disease seems small.

Cyclophosphamide-induced lung disease, as seen in the patient presented here, may go unrecognized with potentially devastating consequences. When interstitial infiltrates develop in these patients, diagnostic considerations are infection, a flare-up of disease, neoplastic disease, oxygen toxicity, and drug effect. Many cytotoxic agents besides cyclophosphamide are capable of causing interstitial lung disease. These include azathioprine, bleomycin sulfate, busulfan, melphalan, and methotrexate.[41] Two reports in 1967 implicated cyclophosphamide as a cause of interstitial lung disease,[42,43] and subsequent observations have confirmed this association.[44,45] Symptoms occur from 1 to 36 months after starting treatment with cyclophosphamide, at total doses ranging from 3 grams to more than 200 grams. Notably, symptoms may persist or progress despite discontinuing the use of the drug. Chest radiograph findings are nonspecific, often showing diffuse linear densities or, occasionally, reticulonodular infiltrates. Pulmonary histologic findings consist of atypical alveolar and bronchial cells, usually with proliferation of type II pneumocytes. Also present are varying degrees of fibrosis and mononuclear cell infiltration.

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Epitomes
Important Advances in Clinical Medicine

Allergy and Immunology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in allergy and immunology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy and Immunology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Platelet-Activating Factor

PLATELET-ACTIVATING FACTOR (PAF) is a potent phospholipid mediator of hypersensitivity and inflammatory reactions that may be important to the pathogenesis of allergic and inflammatory disorders. It is structurally distinct from leukotrienes and prostaglandins, but the synthesis of these lipid mediators of hypersensitivity may be linked. Platelet-activating factor is synthesized by human cells important to allergic diseases, including mast cells, neutrophils, monocytes, and endothelial cells. Increased quantities of PAF are released into the sputum of patients with asthma and chronic lung disease, nasal secretions and skin after antigen challenge, and blood after cold challenge of patients with cold-induced urticaria. Severe childhood asthma is associated with a deficiency of the specific acetylhydrolases that metabolize PAF.

Platelet-activating factor has the novel capacity to induce biphasic or prolonged hypersensitivity reactions in vivo. Its inhalation by humans induces eosinophil influx and transient bronchospasm, followed by prolonged airway hypersensitivity that may persist for weeks. Airway eosinophilia and hypersensitivity are hallmarks of asthma, further suggesting that PAF contributes to the development of asthma. Intradermal PAF induces an acute wheal and flare reaction that subsides and is followed by an erythematous, indurated papule. Its capacity to induce such complex reactions may result either from the wide range of PAF target cells, including eosinophils, neutrophils, monocytes, and endothelial cells, or from complex interactions between PAF and inflammatory cytokines including interleukin-1 and tumor necrosis factor.

Potent, specific PAF antagonists are available and have revealed a critical pathophysiologic role for PAF in some animal models of allergic asthma, anaphylaxis, immune complex disease, and septic shock. Platelet-activating factor antagonists have not yet been tested systematically in human diseases, but preliminary reports suggest that they may be important agents in treating asthma and other hypersensitivity disorders.

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House Dust and Mites

THE HOUSE DUST MITES *Dermatophagoides farinae, Dermatophagoides pteronyssinus,* and *Euroglyphus maynei* of the family Pyroglyphidae are major sources of multiple allergens in homes. Because mite allergens are continuously produced or linger in the home environment as seasonal breeding mite populations die, mite-induced allergic diseases are more perennial or nonseasonal than other airborne seasonal allergens such as pollen and mold.

Detailed analyses of house dust from homes in the United States, Europe, and England indicate that many species of mites can be found in the dust in homes. These include plant and animal parasites and predaceous, saprophagous, and stored-product, soil, and fungal-feeding mites. Of this large array, in most homes in geographic areas where true pyroglyphid "house dust mites" are prevalent, *D farinae, D pteronyssinus,* and *E maynei* make up 90% to 100% of the mites found in dust samples from mattresses, carpeted floors, and fabric-covered overstuffed chairs and couches. These mites are most prevalent in high-use areas where human skin scales collect and serve as a source of food.

The percentage of homes containing *Dermatophagoides* species and *Euroglyphus* species is determined by the characteristic relative humidity in a geographic area. In humid geographic areas such as Ohio and similar locations, nearly 100% of homes have mites, and mite densities may be as high as 18,000 mites per gram of dust. In drier climates, such as Denver, fewer than 10% of homes have mites and mite levels are generally well below 100 mites per gram of dust.

In temperate regions, mite density has a seasonal cycle, with high mite levels occurring in the summer or early fall during periods of high relative humidity and lowest mite levels recorded during the dry heating season. The seasonal cycle may be less pronounced or nonexistent in warmer, humid climates; in some locations several density peaks may exist. In drier climates, mattresses are the primary mite foci, where perspiration and evaporative water from the human

body provide them with a source of water. In more humid climates, carpets and couches contain the largest populations because of the constant availability of moist ambient air.

The prevalence of the three major species of mites varies both geographically and between homes in the same geographic area. Most homes are inhabited by more than one species. In coinhabited homes, one species is generally the most prevalent, but the dominant species varies between homes and also between geographic areas.

Because of their cosmopolitan occurrence and the varied patient exposure to multiple species, this ecologic information is of clinical importance in evaluating patients and also in selecting or assessing effective immunotherapy.

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Venom Immunotherapy

IN THE TEN YEARS since the Food and Drug Administration approved immunotherapy with venoms and venom sac extracts as the treatment of choice for stinging insect hypersensitivity, many groups have reported that only 3% to 5% of venom-treated patients have systemic allergic reactions with subsequent stings, compared with 60% of untreated adults. By contrast, children whose reactions, including urticaria and angioedema, have been confined to the skin appear to have only about a 10% risk of a reaction if stung without immunization; most of those children who do have a reaction when stung have reactions no worse than their original one. A summary of indications for venom immunotherapy includes any systemic manifestation of hypersensitivity in an adult, any extracutaneous manifestation of systemic reactivity in a child, and positive skin tests or radioallergosorbent tests to venom(s).

The success of immunotherapy is judged by the failure to react systemically to a challenge sting. Because the risk of failure of therapy is so small, some authorities think that routine monitoring of venom-specific immunoglobulin (Ig) G antibody levels (whose rise is associated with the appearance of immunity to sting reactions) is unnecessary. Nevertheless, the risk of treatment failure when the antivenom IgG level is less than 0.003 grams per liter is 16%, compared with 3% in patients with IgG values greater than 0.003 grams per liter. When necessary, IgG levels can often be increased by increasing the venom dose to 200 μg per injection of each relevant venom or increasing the frequency of injections.

It is still unknown how long venom immunotherapy should be continued. A high antivenom IgG value is not a sufficient cause for discontinuing venom immunotherapy because the IgG level will fall after therapy is stopped. If treatment is stopped after two years or less of therapy, the risk of reactions to stings rises to about 25% to 30%. One research center reported that after five or more years of uninterrupted venom immunotherapy, the risk of a systemic reaction to sting challenge one, two, and three years after stopping therapy is small. This has been true regardless of whether skin tests are positive or negative and regardless of the titers of venom-specific IgE or IgG at that point. Even so, the risk of future resensitization is unknown. Before these findings can be generally accepted as guidelines for terminating therapy, the long-term sequelae of stopping venom treatment must be understood.

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Autoimmune Demyelinating Disease

MULTIPLE SCLEROSIS is a demyelinating disease of the central nervous system affecting approximately 250,000 Americans. Although the clinical manifestations are protean, classic features include relapsing or chronic unremitting paralysis. The histologic hallmark is focal areas of demyelination (plaques) within the white matter of the brain and spinal cord. Several lines of evidence indicate that multiple sclerosis is an autoimmune disorder. As with many autoimmune diseases, a susceptibility to multiple sclerosis is associated with certain HLA-D genes—immune response genes that encode the class II molecules of the major histocompatibility complex. These molecules are necessary for antigen recognition by CD4+ lymphocytes. Investigators have found an increased number of class II-bearing cells and a predominance of CD4+ T cells in demyelinating multiple sclerosis lesions.

Experimental allergic encephalomyelitis (EAE) is the prototypic model for autoimmune demyelinating disease. It occurs in certain strains of mice and other mammalian species following immunization with the autoantigen myelin basic protein (MBP), the major constituent of central nervous system myelin. Experimental allergic encephalomyelitis can also be induced by adoptive transfer of MBP-specific CD4+ T cells into naive recipient mice. As with multiple sclerosis, susceptibility to EAE is associated with certain class II genes of the major histocompatibility complex, and antibodies to these molecules can prevent EAE. Further, a predominance of class II-bearing cells and CD4+ T cells is found in the demyelinating lesions of EAE. Individual MBP-specific CD4+ T-cell clones that are class II restricted have been isolated that mediate EAE. These T cells are all descendants from a single clone that causes chronic relapsing paralysis and demyelination. The identification of these clones allowed us to characterize the T cells involved in autoimmune demyelination and to further elucidate the role of the major histocompatibility complex. We found that a limited number of MBP-specific CD4+ T cells cause EAE, and it has been reversed with antibodies to the antigen-specific receptors on these T cells. As in patients with EAE, T cells bearing a restricted number of T-cell receptors have been found in the brain and cerebrospinal fluid of patients with multiple sclerosis.

Contemporary therapies for multiple sclerosis focus on modalities that have been effective in other autoimmune dis-

eases. The use of cyclophosphamide, total lymphoid irradiation, and the use of synthetic copolymers are all promising experimental approaches to the treatment of multiple sclerosis. Therapy with monoclonal antibodies directed against specific T-cell subsets and T-cell receptors holds promise.

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Spacers and Reservoirs in Delivery Systems

SPACERS AND RESERVOIRS were developed to aid the delivery of drugs from metered-dose inhalers. These devices, which are attached to the inhalers, should hold the aerosolized spray, making synchronizing between a metered-dose inhaler actuation and inhalation less critical; allow aerosolized droplets to evaporate to a fine mist, delivering the maximal amount of drug to the lungs; and decrease oropharyngeal deposition. β-Adrenergic agonists delivered by metered-dose inhalers in doses of as much as six times those normally recommended, with or without a spacer, give bronchodilation equivalent to nebulizers in patients with acute and chronic asthma, except in some patients with severe asthma.

Delivery to the lung of a whiff by a metered-dose inhaler—at most 15% of each dose—can be improved by holding the inhaler 3 to 4 cm from a wide-open mouth (some authorities prefer the lips to be closed around the mouthpiece), triggering the inhaler during a slow, deep inhalation over five seconds followed by a ten-second breath-hold. Spacers help improve delivery of a drug in a third to half of those patients who cannot correctly use a metered-dose inhaler but add little further therapeutic effect in patients using a proper inhaler technique.

With β-adrenergic agonists, larger spacers with a volume of 750 ml improve bronchodilator response more than smaller spacers. Five spacers are currently available in the United States: Brethancer (Geigy) and Azmacort (Rorer Pharmaceuticals) tube spacers (80 ml and about 100 ml volume) are specifically for terbutaline and triamcinolone metered-dose inhalers; universal add-on devices available are the AeroChamber (Forest Pharmaceuticals), a rigid tube (145 ml); InspirEase (Key Pharmaceuticals), a collapsible bag; and Inhal-Aid (Key Pharmaceuticals), a rigid reservoir (both 700 ml). Other spacers with a pear or cone shape, with about a 750-ml volume and for which there are favorable studies, are not available at present.

Studies with β-adrenergic agonists using Brethancer, AeroChamber, and InspirEase show considerable variation in the effectiveness of these devices relative to a metered-dose inhaler alone. Children using isoproterenol in a metered-dose inhaler with Inhal-Aid achieve bronchodilation equal to that with the use of isoproterenol by intermittent positive pressure breathing. The Azmacort tube spacer, InspirEase, AeroChamber, and Brethancer decrease oropharyngeal deposition, and the latter two have been shown to decrease oropharyngeal thrush from inhaled steroids. AeroChamber has been shown to decrease the dysphonia from inhaled beclomethasone dipropionate.

Physicians should have patients demonstrate their inhaler technique. If it is inadequate or if oropharyngeal thrush or dysphonia from inhaled steroids is a problem, then a spacer, used properly, may be of benefit.

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Methacholine Inhalation Challenge for Diagnosis of Asthma

ASTHMA IS RECOGNIZED CLINICALLY by reversible airway obstruction and airways hyperreactivity. Since the 1940s, bronchial inhalation challenges with pharmacologic and antigenic substances have been used to detect airway hyperreactivity. Bronchoconstriction in patients with asthma can be induced by methacholine, acetylcholine, histamine, carbachol, pilocarpine, serotonin, propranolol, methoxamine, adenosine, prostaglandin D_2 or $F_{2\alpha}$, and leukotrienes C_4 and D_4. Of these, methacholine chloride (Provocholine [Hoffmann La Roche]) has recently been approved by the Food and Drug Administration for inhalation to identify the presence of bronchial hyperreactivity. Methylcholine, a β-methyl homologue of acetylcholine, stimulates the muscarinic receptors on bronchial smooth muscle, increasing bronchomotor activity. Although airways hyperreactivity is present in asthma, the diagnosis is generally made from a combination of history, physical examination findings, and the results of spirometry. Methacholine inhalation challenge is indicated only when the usual evaluation is not diagnostic, such as with patients who have vague symptoms or symptoms such as cough, episodic chest tightness, or atypical dyspnea with normal physical findings and spirometric values. Bronchial challenge may also be used to identify workers who are at risk of occupational asthma developing because of preexisting bronchial hyperresponsiveness. As a research tool, bronchial challenges help clarify the mechanisms of asthma and evaluate new drugs.

Standard procedures for inhaling methacholine have been developed. Factors that influence the response to challenge, such as viral or bacterial respiratory tract infections and pollutants, should be avoided. Various drugs influence the outcome of a challenge, including bronchodilators, cromolyn sodium, and antihistamines. To be challenged, a person should have a baseline forced expiratory volume in one second (FEV_1) of at least 70% of the predicted value. Challenge is done by diluting methacholine from a dry powder and having the patient inhale aerosolized methacholine in ascending concentrations ranging from 0.025 mg per ml of methacholine to 25 mg per ml. Two methods of inhalation are used: five breaths are inhaled from a DeVilbiss nebulizer 646 with a Rosenthal-French dosimeter (0.65 delivery time); or 3 ml of methacholine solution are placed in a

Wright nebulizer and the aerosol is administered continuously for two minutes. After each serial concentration, FEV_1 values are determined, and the procedure ends when there is a 20% or greater fall in the FEV_1 value compared with baseline. Results are expressed as either the provocative dose of methacholine producing a 20% decrease in FEV_1 (PD_{20}), the cumulative dose in breath units (1 breath unit = 1 inhalation of 1 mg per ml of methacholine) producing a 20% decrease in FEV_1, or the area under a dose-response curve. More than 90% of those with asthma respond to methacholine by 200 breath units. Bronchoconstriction following the inhalation of methacholine may also develop in persons with allergic rhinitis, chronic bronchitis, bronchiectasis, and cystic fibrosis, indicating airways hyperreactivity; the provocative or cumulative dose is often larger, however.

Methacholine challenge can be associated with severe bronchoconstriction and should be administered only if oxygen, resuscitation equipment, and inhaled and parenteral bronchodilators are available. It is not a test for routine office use but a useful tool for the evaluation of a person with unexplained respiratory tract symptoms.

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Management of Chronic Idiopathic Urticaria

URTICARIA (HIVES) IS A PRURITIC MIGRATORY ERUPTION characterized by edematous, erythematous wheals of various sizes in the superficial dermis. The term "chronic" refers to symptoms of six weeks' duration or more. Angioedema is a similar reaction confined to the deeper dermis and subcutaneous tissue. The causes of urticaria and angioedema include food, drugs, infection, inhalants, bites and stings, contactants, physical agents, neoplasms, connective tissue disease, and psychic factors. Fatalities from laryngeal edema have been limited almost exclusively to patients with hereditary angioedema and edema due to Hymenoptera stings. Allergy immunotherapy can also result in death. The cause of chronic urticaria usually is not known, hence the term chronic idiopathic urticaria.

For this discussion it is assumed that possible causes have been considered and avoidance has been attempted. Such avoidance may include a diet free of salicylates, benzoic acid derivatives, and tartrazine yellow No. 5, although their potential role in the etiology is controversial. Additionally, potentiating factors such as alcoholic drinks, aspirin, exertion, and heat generally should be avoided. Most patients respond to symptomatic therapy, of which antihistamines of the H_1 inhibitor type are the therapeutic mainstays. Hydroxyzine hydrochloride (Atarax, Vistaril), diphenhydramine hydrochloride (Benadryl), and cyproheptadine hydrochloride (Periactin) are the most effective. Of the three, hydroxyzine is the most potent, with recommended doses starting at 10 to 25 mg four times a day with upward titration. With excessive daytime sedation, 25 to 100 mg can be given at bedtime. Terfenadine (Seldane) with doses as high as 60 mg taken four times during the day can be used in combination with the more sedating H_1 antihistamines. Astemizole (Hismanal) just became available in the United States. It has an exceptionally long duration of action. This and another agent under investigation, ketotifen fumarate, might prove to be useful in refractory patients. Combination therapy should be attempted when single agents are insufficient. Cimetidine, an H_2 blocker, in combination with the H_1 antihistamines, can prove more effective than an H_1 antagonist alone in certain patients. Doxepin, an antidepressant with both H_1- and H_2-blocking properties, is potent in vitro and in vivo and can be given at doses of 25 to 75 mg at bedtime.

Sympathomimetic agents such as terbutaline sulfate, 2.5 to 5 mg three times a day, can supplement the antihistamines. In this respect it should be recalled that patients with acute, severe urticaria or angioedema often respond to subcutaneously administered epinephrine, 0.3 ml of 1:1,000 solution for adults. If the disease is severe and not responding to other forms of treatment, corticosteroids may prove useful. After an initial oral boost such as 45 to 60 mg daily for three to six days, tapering and alternate-day doses, such as 15 to 20 mg every other day, sustain the beneficial effect. Continuous steroid therapy is rarely necessary.

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Asthmogenic Drugs

ASTHMA IS A MULTIFACTORIAL DISEASE characterized by abnormal bronchial reactivity and may be perceived as wheezing, cough, chest tightness, or shortness of breath. Drugs may affect this hyperreactivity by any of several mechanisms. For example, drugs may alter bronchial reactivity through an immunoglobulin (Ig) E-mediated allergic mechanism or by the direct pharmacologic effect of a drug. We will focus on the second group of adverse reactions because they are repeatedly implicated in provoking occult or quiescent asthma and in increasing the severity of established asthma.

Foremost in this drug class are the β-adrenergic receptor blockers, which produce bronchoconstriction by directly blocking the β-receptor on the bronchial smooth muscle. This group currently has three main subclasses in clinical use: nonselective β-blockers such as propranolol or nadolol; β_1-selective (cardioselective) β-blockers—metoprolol, atenolol, for example; and β-blockers with intrinsic sympathomimetic activity, that is, partial agonists such as pindolol. All three classes have been shown to produce deleterious effects. Clearly, the first class produces bronchospasm at the lowest levels and should be avoided in patients with asthma wherever possible. The second was introduced partly because of this limit within the first class. The degree of effect on the β_1- versus β_2-receptors is relative, however, and a large enough dose of a selective drug will still produce significant β_2-blockade. The properties of the third group are less clear;

reports of a significant effect on pulmonary function conflict with studies that find no adverse effects. With any of the three classes of β-blockers, the need for administering the drug to a patient must be carefully weighed against the clear theoretic and observed untoward effects. An additional caveat is that timolol, a β-blocker used as an eye drop in glaucoma, is capable of inducing an asthmogenic response. Betaxolol hydrochloride (Betoptic), a β-selective eye drop, appears not to have a similar systemic effect and might be a safe substitute.

Aspirin, along with many other nonsteroidal anti-inflammatory drugs, has been shown to produce asthma in selected patients. These agents are presumed to work by inhibiting the synthesis of certain prostaglandins, with subsequent shunting of the parent prostaglandins through alternate pathways. Nonsteroidal anti-inflammatory drugs that are cross-reactive with aspirin include ibuprofen, indomethacin, piroxicam, naproxen, and meclofenamate sodium, along with several others. The asthmogenic effects of aspirin can be seen in between 4% and 10% of asthmatic persons, who should avoid its use, and in a large number of so-called triad patients with asthma, nasal polyposis, and aspirin sensitivity. Rare reports of hydrocortisone succinate producing asthma in aspirin-sensitive patients warrant avoiding its use in these patients. Other steroids seem not to have this effect. There are many previous reports of a cross-reactivity between aspirin and tartrazine dyes, but these have not been rigorously confirmed and may not, in fact, be real.

Angiotensin-converting enzyme inhibitors such as captopril and enalapril maleate have been shown to produce cough as a side effect, which can mimic uncontrolled asthma. The pharmacologic mechanism is uncertain but is thought to be related to bradykinin metabolism and possibly with its role in axonal transmission. These agents are reported to also alter bronchial reactivity, so the cough may indeed be produced by this mechanism. The incidence of cough is low, with estimates varying from 1% to 14%, and is often reported after prolonged use of the drugs.

Incidents of asthma following many other therapeutic interventions are reported on a scattered basis. Mast cell degranulation by an unclear but non-IgE-mediated mechanism can lead to bronchospasm. Examples of drugs that act in this manner include iodinated dye and opiates—especially codeine and morphine. Inhaling acetylcysteine can cause broncho-spasm, presumably by a primary irritant effect. The same has been reported for sympathomimetic aerosols, especially isoproterenol. Rare reports of bronchospasm from cromolyn sodium can be found, and, again, bronchospasm is probably due to primary irritation. Also, agents that alter lower esophageal sphincter tone and increase gastric acid secretion can lead to reflux, which may produce nocturnal cough easily mistaken for asthma.

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Editorials

Thoughts on Rationing Medical Care

THE OREGON EXPERIENCE described by Crawshaw and colleagues elsewhere in this issue brings into sharp focus what happens when the dollars available for high technology patient care simply do not meet the need. The state of Oregon is prohibited from borrowing money for public services, and there is no sales tax. The state cannot spend money that it does not have. When a young boy on the Medicaid program needed a bone marrow transplant to treat his leukemia, the money simply was not there. The boy died and there was an outcry. In their update of the Oregon approach to this and other ethical problems in health care, Crawshaw and associates describe one option for dealing with the inevitable rationing that will be needed, particularly for expensive high technology patient care.

Given that scientific progress has occurred and will continue to occur, and given that finite resources will never be able to satisfy infinite demands and expectations, some rationing of patient care is inescapable. At present the approach is, to say the least, crude and insensitive. It is to let the economic winds prevail. If you can pay for it, you can have it, and the corollary is that if you cannot pay for it, you do not get it. The tragedy is that with this approach the poor fall between the cracks and are unfairly disadvantaged in that they are deprived of what can be had by those who have access to the resources that are available. This becomes a serious disadvantage in view of deregulation of health care in the private sector and reduced funding of increasingly regulated care in the public sector. The private sector cannot be expected to be in business to finance care for the poor, and the government can no longer afford to finance equal access to care for those who cannot pay for it. This is patently unfair and in many ways may not even be good public policy.

When one thinks about it, rationing means that someone has to decide what resources will be available for care, and someone has to decide who gets what. These decisions are de facto being made now by the payers in the private sector—business, industry, insurance—and by federal, state, and local governments. They decide what their dollars can or will pay for and what they can or will not. In spite of rhetoric to the contrary, all these payers are of necessity self serving, leaving patients who do not have their own resources at a disadvantage when they need expensive care—that is, when their own self-interest is involved. In this situation the power lies where the dollars are, and the public, not to mention patients, has little to say about how many dollars will be available for health care in any state or any community, or how these dollars will be used. The fact is that the self-interest of patients or the public has little chance for expression or influence.

In the final analysis it is the consumer, patient or not, who pays for all health care in one way or another and who has the most at stake in whatever is done or not done about rationing it. How can consumers, or the public, be involved meaningfully in the decisions that are made, decisions that may come to affect their lives so personally? Are these decisions really too important to be left to self-interests, whether in the public or private sectors of society? It is in this connection that the Oregon experience, or perhaps it should be called an experiment, seems so important. Under the leadership of Crawshaw and colleagues, the principle of the town meeting is being adapted to develop community-based citizen discussion and recommendations concerning some of the "life and death" decisions that are necessitated by modern medicine. Oregon Health Decisions and Citizens' Health Decisions, USA should be followed with interest. They just might be on the right track.

MSMW

Pertussis—A Disease and a Vaccine That Are Not Going Away

IN MARCH 1982, diphtheria and tetanus toxoids and pertussis vaccine (DTP) cost about 15 cents per dose for public sector providers and 37 cents for private sector providers. There were three vaccine manufacturers. The vaccine that had come into routine use in pediatric practice during the late 1940s and early 1950s was considered the major cause of a dramatic reduction in the number of reported pertussis cases from an annual average of 110,847 cases reported between 1945 and 1950 to 1,248 cases reported in 1981. Intermittent controversy about vaccine safety in the medical community had been raised almost since pertussis vaccines were developed in the 1930s, and alternative vaccines had been sought.[1] In April of 1982, a television program entitled "DPT—Vaccine Roulette" aired in Washington, DC, and was excerpted on the "Today" show. The program ignited a controversy about the risks and benefits of whole-cell pertussis vaccines among the United States lay public that had flared in the United Kingdom and Japan since the mid-1970s. Since 1982, the debate has become more acrimonious. Between 1978 and 1981, an average of about two lawsuits alleging damage from the vaccine was filed annually against DTP manufacturers. Between 1982 and 1986, the number of lawsuits filed increased dramatically, peaking at 255 in 1986. Vaccine prices have paralleled the increase in lawsuits.[2] As of February 13, 1989, the price of DTP was $8.46 for public providers and $11.03 for private providers. One of the three manufacturers dropped out of the market in 1984.

Two issues are at the heart of the controversy. First, do the benefits of vaccine truly exceed the risks? Second, if the benefits exceed the risks, why are the risks "so high"—why do we not have a better, safer pertussis vaccine?

The controversy about benefits concerns whether pertussis disease is serious enough to merit prevention and whether whole-cell pertussis vaccine is truly effective. Are the morbidity and mortality from pertussis disease significant? As noted by Cherry and co-workers elsewhere in this issue, complications from pertussis such as pneumonia and seizures are frequent among reported cases, particularly in the very young. Although these data may be skewed somewhat toward more severe cases, even those who think that pertussis is a trivial disease quote hospital admission rates of 1% or higher.[3] This is not the characteristic of a benign disease.

Although the efficacy of some whole-cell vaccines was demonstrated in the United States, it was established most convincingly in trials conducted by the Medical Research

Council in the United Kingdom in the 1950s. An efficacy of 70% to 90% was reported.[4-6] Subsequent studies in the United States have generally confirmed the Medical Research Council's results.[7] In general, those studies using the best methodology, such as requiring culture confirmation as part of the case definition, have shown the highest vaccine efficacy. Recent data on vaccine efficacy in the United States based on the secondary attack rate in families have shown an efficacy of 89% when adjusted for age.[8] As noted by Cherry and associates, efficacy is also apparent from the acceleration of the decline in pertussis incidence rates following the introduction of vaccine and from the resurgence of cases of pertussis in the United Kingdom and Japan when coverage dropped dramatically.

Thus, most health authorities strongly believe that this disease should be prevented, and data from currently available whole-cell vaccines in both the United States and the United Kingdom indicate the disease can be prevented and well controlled in large populations.

What are the risks from pertussis vaccine, and how frequently do they occur? As pointed out by Cherry and colleagues, the pertussis component of DTP appears to be responsible for a number of common local and systemic effects including local reactions and fever seen following the administration of DTP. Although most vaccinees probably experience some side effect, the common reactions are transient, leaving no known residua. Of more concern are the uncommon adverse events of persistent inconsolable crying, abnormal high-pitched crying, seizures, and hypotonic-hyporesponsive episodes. To date, it has not been proved that inconsolable crying and high-pitched crying in association with DTP represent neurologic abnormalities that could result in permanent damage. Most seizures are probably attributable to the fever induced by DTP. A follow-up of children suffering seizures as reported by Baraff and co-workers suggests little, if any, permanent residua.[9] Similarly, their limited data suggest that hypotonic-hyporesponsive episodes also do not appear to be associated with lasting effects. Such episodes should not automatically be attributed to the pertussis component of DTP since episodes characterized by similar clinical manifestations have been reported after the administration of diphtheria and tetanus toxoids.[10]

The greatest attention and concern have been focused on the very rare but serious neurologic illnesses that occur in temporal association with DTP administration and their potential for neurologic damage. As noted by Cherry and associates, following the report of the National Childhood Encephalopathy Study (NCES), the only large-scale controlled evaluation of the relationship of DTP and serious neurologic events, the medical community generally accepted the fact that DTP could cause significant neurologic damage lasting at least a year. Nevertheless, such events attributable to vaccine were exceedingly rare, 1 in 330,000 doses administered, and the estimate of damage was imprecise, with 95% confidence limits ranging from 1 in 50,000 doses to 1 in 18,000,000 doses.[11] As pointed out both by Cherry and colleagues and the investigators of the NCES, caution is required in interpreting the data.[12] The results, not of a new study or scientific review but of a court case in the United Kingdom, have recently reopened the question. In *Loveday versus Renton, Wellcome, et al,* a judge heard comprehensive testimony from both renowned proponents and opponents of pertussis vaccine as a cause of serious neurologic damage.[13] The judge evaluated multiple criteria for causation including an examination of whether there was a specific clinical syndrome, a specific pathologic disorder, whether data from animal models were useful, plausible biologic mechanisms, and the results of various studies with major reliance on the NCES. Original data on selected individual cases from the NCES were reanalyzed. In a comprehensive review, he concluded that there was insufficient evidence to implicate the vaccine in causing permanent neurologic disabilities. The judge's findings suggest that a scientific reevaluation is needed. For the present, we continue to use the NCES estimates when informing parents or guardians of prospective vaccinees about potential risks of pertussis-containing vaccines. In the NCES study, investigators reported that the incidence of serious neurologic illnesses attributable to pertussis disease significantly exceeded the incidence attributable to pertussis vaccines, 1 case in 11,000 cases of disease versus 1 case in 140,000 doses of vaccine administered.[11]

All formal risk-benefit analyses done to date in the United States have shown that the benefits of pertussis vaccine exceed the risks.[14] In the absence of alternative licensed vaccines, the major immunization advisory bodies continue to strongly recommend the routine use of whole-cell vaccines.[15,16] Nevertheless, there is a strong desire for safer and equally effective pertussis vaccines. The hope is that such vaccines would reduce the occurrence of the rare but potentially most serious adverse events and help restore public confidence that has been shaken by the reports of serious vaccine reactions.

New vaccines are also needed because adults are being increasingly recognized as sources of infection for young children. Pertussis outbreaks involving older children and adults have been extremely difficult to control because only antibiotics are recommended to curtail transmission among persons 7 years of age or older. Massive erythromycin use is not a practical measure for controlling community-based outbreaks. Because of the toxicity and difficulties in assuring widespread compliance, its use is generally limited to preventing household transmission. Thus, as noted by Cherry and co-workers, a vaccine that could be used for both primary and booster immunization of adults would represent a significant addition to our armamentarium for preventing pertussis.

If so potentially useful, why has no improved component pertussis vaccine been licensed in the United States? Efforts have been made to develop improved pertussis vaccines for many years.[1] A major development occurred in Japan when component vaccines consisting primarily of detoxified lymphocytosis-promoting factor (pertussis toxin, LPF) and filamentous hemagglutinin (FHA) were developed and licensed for use in 2-year-old children in 1981.[17] While no formal controlled evaluations were undertaken, observational studies have reported the efficacy of a three-dose series as approximately 90% in these children. The widespread use of vaccines has led to substantial decreases in the incidence of reported pertussis in all age groups. The incidence among children younger than 2 years, however, an age group that is not routinely vaccinated, was still severalfold above the reported incidence rates in this age group when whole-cell vaccines were in widespread use.

The absence of data from Japan on vaccine efficacy and safety in infants, the group most in need of vaccine, made the Swedish vaccine trial of Japanese vaccines (LPF alone and

LPF plus FHA) in infants 5 to 11 months of age extremely important.[18] Data on product-specific safety and efficacy will be needed for any product being considered for approval in the United States.

The results of the Swedish trial have been both helpful and perplexing. For the first time, evidence of the efficacy of a licensed Japanese vaccine has been shown in a placebo-controlled trial among infants, and for the first time a detoxified LPF alone was shown to be effective in children. However, the estimates of efficacy from this "gold standard" trial were less than those previously reported with whole-cell vaccines, although the later studies were not as methodologically rigorous and a true direct comparison is not possible and, if made, may be misleading. A direct comparison would have required using a whole-cell vaccine in the Swedish trial. Also, in contrast to the multidose schedules currently recommended in Japan and the United States, a two-dose schedule was adopted in Sweden based on immunogenicity studies in which levels of antibody thought to be protective by the investigators were achieved after two doses separated by an interval of two months.[19] A third dose could potentially have raised efficacy estimates. Further, as noted by Cherry and associates, the failure to correlate serum antibody levels with protection against disease makes testing of other vaccines as well as monitoring quality control difficult and suggests there is a need for further study.

Additional data on safety and efficacy, as defined in studies of households, continue to be generated in Japan. These, combined with the efficacy data obtained from infants in Sweden, may result in an application for licensure in the United States of one or more acellular vaccines. Safety and serologic data are being obtained by different manufacturers for other types of products as well. The adequacy of the total body of data submitted in support of any license application must await a formal review by the Food and Drug Administration and their advisory groups. In the meantime, additional well-controlled studies, particularly comparative efficacy studies of whole-cell and different acellular vaccines, should be vigorously pursued. Until new vaccines are licensed, we will continue to need whole-cell vaccines. We can control the disease with the present vaccine, but until we have a vaccine that can be used in persons older than 6 years, we can expect to see continuing limited outbreaks of pertussis.

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A Critical Moment in Our History

As a nation we seem now to have lived through eight years of what some might call a time of wishful thinking, something akin to a pleasant dream. Any unpleasantness was largely ignored, or in a sense swept under the rug. We seemed actually to put our faith in the fantasy rather than in any reality of "star wars," as the Strategic Defense Initiative was dubbed. And at the end of the eight years, the polls showed almost unprecedented public approval of the way the Presidency had been conducted, and the electorate confirmed or even strengthened the political status quo. It appears that the Republicans continue to have a relatively secure hold on the White House and the Democrats have gained what seems to be almost permanent control of the Congress.

For better or worse, a major and enormously expensive commitment of national resources was made to assure that our nation would be militarily strong, and perhaps a fear that the Soviets could not compete either economically or militarily may have changed the minds of the Kremlin leadership and caused them to alter their policy of confrontation with the nations of the western world. This was a very major gain and possibly even worth the cost. But there has been a downside to this eight years of studied optimism and of military and political achievement. As a nation we have been losing ground to our own economic competitors in the western world, and there is disturbing evidence that our standard of living is not what it was even a few years ago. Servicing the national debt, the continuing federal budget deficits, a negative balance of international payments, and a growing foreign investment in American business and industry, are beginning to take their toll. These, together with the entitlement programs that we have voted to ourselves, have seriously constrained, if not diverted, resources that might now otherwise be available for domestic needs and to prepare us for the even harsher economic competition that may surely be expected in the very near future.

If harsher competition is what lies ahead for us as a nation, as is likely, we must give serious attention to girding ourselves and strengthening our resources for this purpose. The need for adequate education for every citizen seems obvious. We must all at least be literate, perhaps even computer literate. But equally important, and perhaps even more important, no nation can be truly strong unless it is also a healthy nation, and here too there is evidence that we are falling behind, in spite of our acknowledged scientific and technologic leadership in medical care. Many of our youth, particularly our disadvantaged youth, are not receiving either the education or health care they will need to compete successfully in our own society, not to mention to help provide the sinew to make our nation strongly competitive with the rest of the world.

This is truly a critical moment; it could even be a watershed moment in our history. Four or eight years from now may be too late. This is a time for a new realism, and for the kind of collaborative effort among all segments of society that happens best when a country perceives that it is in danger. And there is reason to believe that this nation is now in danger, albeit a different kind of danger than we have known in the past. Education and health, particularly of our youth, are lasting measures of power, and both surely should be top priorities for the new administration.

MSMW

Case Reports

Coin Ingestion Complicating a Tavern Game

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OVER AN 18-MONTH PERIOD, two college students presented to the emergency department at the University of Washington with coins impacted in the esophagus, and one student presented with a coin in the duodenum. All three had been playing a tavern game, "Quarters," which resulted in the coin ingestions. Although well recognized in children,[1-6] it is unusual for adults to ingest coins. "Quarters" has been briefly mentioned in a review of foreign bodies of the upper gastrointestinal tract[1]; yet, it has not been well described nor have cases been reported. Three cases are reported here.

Description of Game

"Quarters" is played with a number of people sitting around a circular table, generally in a tavern. One variation of the game has students drinking as rapidly as possible a glass of beer with a quarter in the bottom and attempting to catch the coin between their teeth. The more alcohol consumed, the more difficult it is to catch the coin. Particularly popular in the Pacific Northwest is a variation that also stresses marksmanship. Contestants bounce coins off the table into opponents' beer glasses. If the coin lands in the glass, the person who is sitting in front of it must drink the beer without swallowing the coin. Yet another variation has a centrally located glass into which players bounce coins. If the coin lands in the glass, the victor drinks it.

Figure 1.—The radiograph shows a quarter lodged at the gastroesophageal junction in patient 1.

(Gluck M: Coin ingestion complicating a tavern game. West J Med 1989 Mar; 150:343-344)

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Report of Cases

Case 1

An 18-year-old college student complained of dysphagia after accidentally ingesting a quarter while playing the described game. A chest radiograph showed the coin lodged in the distal esophagus (Figure 1). Uneventful removal of the quarter from an area immediately proximal to the gastroesophageal junction was achieved using a rat-tooth forceps. No complication was noted, and the patient was discharged later that day.

Case 2

A 23-year-old man presented with dysphagia after ingesting a 50-cent piece while playing "Quarters." Radiographs located the coin in the upper esophagus at the thoracic inlet (Figure 2). The coin was retrieved using the rat-tooth forceps.

Case 3

A 22-year-old woman visited the emergency department on the advice of her friends after she ingested a quarter playing the same game. She was asymptomatic. Radiographs located a coin in the duodenal bulb (Figure 3). Although the quarter was not found on monitoring of her stools, abdominal films seven days later indicated that the coin had passed.

Discussion

Reviews of foreign body ingestions stress that children tend to have impacted coins, buttons, and metallic objects, while adults tend to have impacted meat, bones, and other food substances.[1-6] Those adults who do swallow metal objects are most frequently prison inmates or psychiatric patients.[7] The three young adults presented in this report, therefore, represent another risk group.

Giordano and colleagues noted that 50% of impacted foreign bodies in the esophagus of children were at the thoracic inlet, 17% were in the midesophagus, and 29% in the distal esophagus.[2] The esophageal lumen is externally constricted by the aorta, by the left atrium, and at the diaphragm. Of the cases presented in this report, one patient's coin impacted at the gastroesophageal junction and the other just above the aorta immediately below the thoracic inlet. One patient spontaneously passed the coin through all luminal narrowings, which presumably is what happens with most accidental coin ingestions.

Before the widespread use of flexible endoscopes, rigid instruments were used to remove foreign bodies from the esophagus. Major complications in as many as 9% of patients were reported in one series.[4] It is generally accepted that flexible instruments are the preferred instruments for retrieving most foreign bodies from the esophagus.[1] The two patients who had coins removed endoscopically tolerated the procedure well and without complication. The rat-tooth forceps provided a solid grip, facilitating removal. The patient who had an impacted 50-cent piece was asked to swallow when the coin and endoscope were at the level of the crico-

pharyngeus muscle. The voluntary relaxation of the upper esophageal sphincter allowed the large coin to pass with minimal resistance.

According to students and tavern owners, the game "Quarters" generally results in substantial consumption of alcohol. As the players become more inebriated, they discriminate less well between liquid and solid as they rapidly drink a glass of beer. Furthermore, alcohol reduces both upper and lower esophageal resting and yield pressures.[8,9] When the patients "chug-a-lugged" their beers, a coin could tumble through a poorly responsive pharynx and through a relaxed upper esophageal sphincter to some portion of the esophagus that was sufficiently extrinsically constricted to stop further progression. Alcohol reduces esophageal peristalsis. In the two patients with esophageal impactions, there was no pathologic lesion found to explain the impactions besides the normal anatomic constrictions and the effect of alcohol.

"Quarters" remains a popular game among college students in the Pacific Northwest. The foreign body ingestions are readily treatable either by time or, if impaction is present, by flexible endoscopy. This report alerts physicians to the game and its consequences.

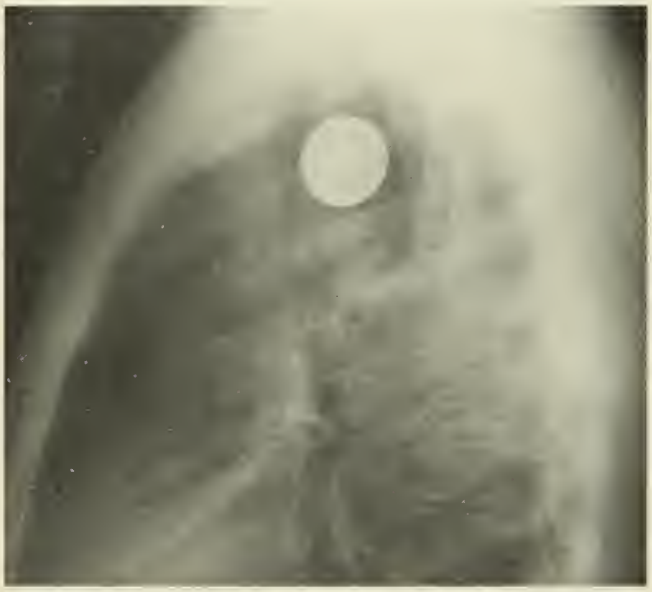

Figure 2.—In patient 2, the ingested 50-cent piece lodged at the thoracic inlet immediately above the aorta.

Figure 3.—A radiograph taken of patient 3 shows a quarter located in the duodenal bulb. The patient was asymptomatic and passed the coin without incident.

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Bleomycin-Induced Pulmonary Fibrosis in a Patient With Rheumatoid Arthritis

A Possible Synergistic Effect?

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BLEOMYCIN is the chemotherapeutic agent most frequently associated with pulmonary toxicity.[1-5] Previous or concomitant radiotherapy to the thorax, concomitant chemotherapy, and high inspired oxygen concentrations may enhance the toxicity of bleomycin, producing a toxic reaction at a lower total dose.[6,7] The effect is dose- and age-related,[1] and life-threatening disease is unusual at total doses of less than 150 units.[3]

We report the case of a patient with rheumatoid arthritis and stage IIIB Hodgkin's disease in whom pulmonary fibrosis developed after he received 137 units of bleomycin. This unexpected toxicity at a relatively low cumulative dose raises the possibility that the patient's rheumatoid arthritis may have made him more susceptible to bleomycin-induced pulmonary toxicity.

Report of a Case

The patient, a 51-year-old man, was admitted to Pacific Medical Center (Seattle) in April 1987 because of dyspnea and cough for three months. On examination he was afebrile. There was no finger clubbing or palpable lymphadenopathy. A chest examination revealed bilateral bibasilar crackles. He had characteristic changes of rheumatoid arthritis involving

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his hands, elbows, shoulders, and knees. Symptoms of his rheumatoid arthritis had not recently worsened. Radiographs of the hands showed subchondral erosions with cystic formation.

The patient had been diagnosed as having gout about 15 years previously on the basis of intermittent inflammatory arthritis of the knees and great toes and persistent hyperuricemia. He had been treated with courses of allopurinol and colchicine with reasonable control. In 1978 he presented with symmetric hand and wrist arthritis with morning stiffness and constitutional symptoms. The diagnosis of rheumatoid arthritis was established on the basis of the findings of a physical examination, a rheumatoid factor of 1:160, and hand x-ray films showing erosions, periarticular osteopenia, and soft tissue swelling characteristic of rheumatoid arthritis. He was treated with a gold compound for eight months and had a remission of his joint and constitutional symptoms. A rash developed at a total dose of 945 mg of gold compound, and this therapy was stopped. In March 1985 the patient again had a flare-up of his rheumatoid arthritis and received a second trial of gold therapy, with redevelopment of a rash. From March 1985 his joint symptoms were managed with ibuprofen therapy. There was no clinical evidence of pulmonary toxicity due to gold therapy or to rheumatoid arthritis.

Figure 1.—A chest x-ray film taken immediately before an open-lung biopsy shows diffuse bilateral interstitial changes.

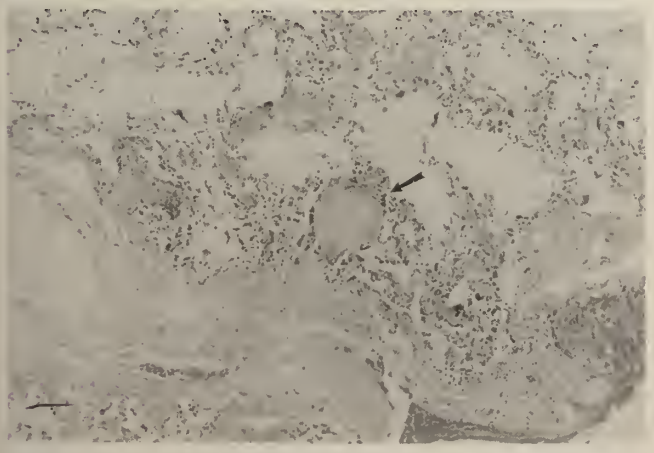

Figure 2.—The biopsy specimen of the left lower lobe of the lung shows areas of active interstitial inflammation **(arrow)** and regions of mature interstitial fibrosis. Little inflammation is present (hematoxylin-eosin, original magnification × 60.5).

The patient was diagnosed with Hodgkin's disease in 1986, nine months before this admission to hospital. He presented with cervical lymphadenopathy and was found to have involvement of the spleen and mediastinal and retroperitoneal nodes. He had been treated with eight courses of mechlorethamine hydrochloride, vincristine sulfate, procarbazine hydrochloride, prednisone, doxorubicin (Adriamycin) hydrochloride, bleomycin sulfate, and vinblastine sulfate (MOPP/ABV). He had received neither supplemental oxygen nor radiation therapy. The cumulative dose of bleomycin was 137 units.

His chest x-ray film (Figure 1) showed decreased lung volumes and abnormal lung parenchyma with diffuse interstitial changes in both lungs for the first time. A radiograph taken immediately before chemotherapy showed a normal lung volume and clear lung fields. Pulmonary function test results indicated progressive deterioration, with a moderate restrictive pattern (total lung capacity 68% of predicted) and a moderate to severe reduction in the diffusing capacity of the lungs for carbon monoxide (42% of predicted). An open-lung biopsy from the left lower lobe was done, and the specimen showed a mixture of acute and chronic changes (Figure 2). There was a background of dense interstitial fibrosis involving pleura and secondary lobular septa. Superimposed on this were nodular areas of active interstitial fibrosis involving alveolar septa, lobular septa, and small confluent areas of lung parenchyma. A few lymphocytes were scattered through the areas of fibrosis, but no eosinophils were seen and neutrophils were rarely seen. There was no evidence of vasculitis or bronchiolitis obliterans. Immunofluorescence studies for immune complexes were not done.

Bleomycin therapy was discontinued from the patient's chemotherapeutic regimen, and a regimen of 60 mg of prednisone daily was begun. The patient continued to deteriorate clinically, however, and two weeks after his open-lung biopsy, he was readmitted to hospital because of progressive dyspnea. There was no evidence of infection, and his chest x-ray film showed no new localized infiltrate. He was afebrile, he had no sputum production, and his blood cultures were negative. He died suddenly within a month of the open-lung biopsy. His death was an acute cardiopulmonary event thought to have been caused by either an arrhythmia or possibly a pulmonary embolus. No autopsy was done.

Discussion

This case shows a recognized complication of bleomycin toxicity at an unexpectedly low dose. We postulate that there may be a synergistic mechanism between rheumatoid arthritis and bleomycin therapy in the pathogenesis of pulmonary fibrosis. Immunologic mechanisms could be responsible for the unusual susceptibility to bleomycin toxicity shown by this patient. Interstitial lung disease has been estimated to occur in 20% to 40% of patients with rheumatoid arthritis. It is often both clinically and radiologically silent. Lung biopsy specimens of patients with rheumatoid arthritis

and interstitial lung disease show immunoglobulin G and complement deposition in pulmonary capillaries.[9] The mechanism is thought to be related to the production of immune complexes, either locally or systemically.

Several mechanisms of bleomycin-related pulmonary injury are suggested. Bleomycin is concentrated preferentially in the lung and is inactivated by a hydrolase enzyme that is relatively deficient in lung tissue. It is unknown whether certain persons are more deficient in this enzyme than others. A second mechanism is that bleomycin may generate reactive oxygen metabolites.[1] Third, there may be a greater influx of polymorphonuclear neutrophils in susceptible persons, thereby causing direct lung injury with their release of oxidants and proteases. Bleomycin has also been shown to affect collagen synthesis inhibitors, resulting in an increase of pulmonary collagen.[1] Finally, it has been noted that bleomycin may stimulate the humoral immune system and that diseases such as rheumatoid arthritis could be exacerbated by an increase in the antibody level. In a rat model of bleomycin-caused lung injury, Struhar and co-workers showed that there was an increase in both the intensity and the distribution of surface antigens of epithelial cells.[8]

There are alternative explanations for the development of pulmonary fibrosis in this patient. He had had exposure to several chemotherapeutic lung toxins in addition to bleomycin. He had recently received procarbazine and vinblastine to treat his Hodgkin's disease.[3] Combination chemotherapeutic regimens are thought to increase the risk of inducing bleomycin pulmonary toxicity.[1] Procarbazine, however, appears to cause a hypersensitivity reaction with eosinophilia,[1] rather than the pattern observed here. Vinblastine used in combination with mitomycin has in rare cases been reported to induce pulmonary fibrosis.[1] In addition, this patient had received gold therapy seven years previously.

In conclusion, a possible mechanism for the apparently increased pulmonary susceptibility to bleomycin toxicity in this patient is complement-mediated immune-complex disease. The simultaneous increase in the surface antigens of the lung epithelial cells induced by bleomycin treatment and a high level of circulating immune complexes—caused by the patient's rheumatoid arthritis—against those antigens may have resulted in severe lung injury. We suggest that patients with rheumatoid arthritis may be more susceptible to bleomycin-induced pulmonary fibrosis by these possible synergistic mechanisms.

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Correspondence

Women and Medicine

To THE EDITOR: It was a delight to read the special December issue on *Women and Medicine,* not only because of the excellent papers but also because of the inclusion of pictures and poetry, symbolizing the marriage of art and science in medicine.[1]

Some of it, of course, made painful reading: the physician who talks, hand on doorknob, about mastectomy as a mere technicality, the assistant dean who reluctantly admits a qualified applicant "although she is a woman," and similar descriptions. But, on the whole, the myth of male superiority and with it the whole concept of "MDeity," is disappearing, none too soon, from the medical scene.

Yet, somehow I wish that art and poetry were not restricted to special issues and were not gender-related. Sooner or later we shall have to learn that what matters in medical practice is not to be a man or a woman but to be what is common to all of us, colleagues and patients alike, namely human. Then, let's have a very special issue of the journal called *Medicine and Humanity!*

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REFERENCE

1. Women and Medicine (Special Issue). West J Med 1988 Dec; 149

* * *

To THE EDITOR: Admittedly, by now I am a member of the older generation, trained in medicine before affirmative anything, comfortable with the traditional face of medicine before Madison Avenue, and, as Emily Friedman put it,[1] "boutique" packaging of health services. As a female physician, I am proud of my role in medicine and pleased to see a generation of excellent female physicians coming behind me, respected for their professional abilities, not their gender. Overall, I was delighted to see the journal recognize the increasing participation of women in medicine and devote its December issue to it.[2]

I was fairly chagrined, however, to see the cover of this issue: nude golden females in a pagan dance, witches yet, announcing the thane of Cawdor, I presume. In my "older" opinion, the cover is inappropriate, in poor taste, and pejorative to women in general and female physicians in particular. Symbolism is important. It will be hard to break through that cover to focus on anything that has to do with professional ability. A portrait of Elizabeth Blackwell would have been more to the point.

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To THE EDITOR: I am writing in response to the article "Women and Breast Cancer" that appeared in the December issue.[1] Having completed chemotherapy and radiation treatment for breast cancer this past year, I found Myrna Frankel's article a realistic and succinct discussion of most of the key issues women with breast cancer must face. Although my personal experience with physicians and other health professionals appears to have been more supportive and less defensive than the author's, her portrayal of individual and institutional denial of death and pressure to be the "good" (passive) patient was right on target.

I was struck by the seeming necessity to justify inclusion of this article in the introductory remarks by the guest editor, Dr Clever. The fact that such inclusion was controversial because some considered the article expressed "unrelieved anger" or lacked "balance" underscored one of the major points of the article itself—how out of touch some physicians are with the patient's perspectives and experiences.

Based on our experiences these past 18 months, both my husband, a physician, and I thought that reams could be written on each of the many points the author so concisely presented. Frankel did an excellent job of covering much of the territory and, it is hoped, has sensitized some professionals to a fuller view of the realities that confront breast cancer patients.

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REFERENCE

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Nonsuppurative Pericardial Effusion

To THE EDITOR: The case report by Drs Horton and Tucker in the August 1988 issue described a unique finding of nonsuppurative pericardial effusion occurring as a result of left subdiaphragmatic abscess.[1] The finding is considered unique presumably because manual searches of standard medical literature bibliographic compilations *(Quarterly Cumulative Index, Quarterly Cumulative Index Medicus, Current List of Medical Literature, Cumulated Index Medicus)* from 1916 through 1965, "and a computerized search of *Cumulated Index Medicus* from 1966 through 1986 uncovered no references of direct relevance."

Horton and Tucker point out that in contrast to their four cases of nonsuppurative sympathetic pericarditis, the pericarditis cases that have been reported as complications of subdiaphragmatic abscess in the past 50 years have been suppurative in nature (with one possible exception reported in a 1958 publication). In addition, on the basis of their experience, they postulate an association between nonsuppurative pericardial effusion and left subdiaphragmatic abscess.

Because of the inability of the literature searches to locate other pertinent references and to insure that whatever priorities are involved are viewed in appropriate perspective, I call to your attention two case reports that I found in my reprint files that have direct relevance, in that they are both cases of nonsuppurative pericardial effusion in association with subdiaphragmatic abscess. In addition, in contrast to the left-sided association mentioned above, one of the cases I shall mention seems to have been associated with a right-sided abscess, because of a finding of a raised and immobile right side of the diaphragm.[3]

One case was described at a clinicopathological conference at Barnes Hospital (Washington University School of Medicine, St Louis). Autopsy findings were, among other things, right and left subdiaphragmatic abscesses, subhepatic abscess, bilateral empyema, cortical necrosis of the right kidney, infarction of the left kidney, and fibrinous pericarditis.[2] Horton and Tucker's case 4 was found at autopsy to have a fibrinous pericarditis with clear amber pericardial fluid having been obtained premortem, with no fluid culture or cell counts done. In the Barnes Hospital case the pathologist described the pericarditis as uremic, with no pus or organisms in the exudate; the pericardial fluid was bloody.

The second case, reported some four decades ago,[3] was an 11-year-old boy who, 5½ months after gangrenous appendectomy followed by subdiaphragmatic abscess evacuation, was found to have a pericardial effusion that was sterile on culture and receded within a week of aspiration. Three weeks later, it recurred, with fluid of the same character as before being obtained. The patient recovered over the next five days, but effusion developed again two months later (7½ months after the initial surgery). He again made an uneventful recovery. The author of this case report opined, "It is unlikely that there was a direct invasion of the pericardium as the fluid was repeatedly sterile on culture. The effusion is probably analogous to the oedema surrounding any acute inflammation."

Horton and Tucker state that the mechanism for the nonsuppurative pericarditis that occurs in association with subdiaphragmatic abscess is unknown and suggest that changes in capillary permeability or diaphragmatic lymph flow resulting from local inflammatory effects may play some role.

As indicated by the first case I mentioned, uremia may cause a nonsuppurative pericarditis in association with subdiaphragmatic abscess. Furthermore, we should not overlook the intensive antibiotic therapy that was administered for a number of days before aspiration of the pericardial fluid in all cases under discussion here. This might account for the finding of sterile pericardial fluid in clinical situations where obviously profound sepsis was present. If these assumptions are correct, it is likely that more cases of nonsuppurative pericardial effusion have occurred and will occur, given the rapid advances in our diagnostic capabilities and therapeutic weapons.

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Treating Southeast Asian Patients

To the Editor: The Molinas' article in the October 1988 issue[1] about prevalence of parasites among Cambodians was interesting but holds disturbing implications. The high prevalence of intestinal parasites in relatively recent arrivals from Southeast Asia comes as no surprise. The subjects studied had unreliable histories of screening and treatment. Indeed, even the statement that all had been "screened" after arrival to the United States provides little information: no national standards of refugee screening exist. Screening protocols are determined individually by each county and are generally provided only by the first county of residence for the refugee. Thus, there is tremendous variation in the extent to which initial screening of stools of asymptomatic refugees occurs. In those instances where positive stools are identified, determining successful treatment by reexamination of stools is often frustrated by overburdened public clinics and the refugee's subsequent move to another city.

The disturbing evidence the Molinas report is the 42% treatment failure rate. This high rate of noncompliance suggests that there are systematic cultural factors among the Cambodian and Hmong subjects that will provide a tremendous obstacle to treating patients with asymptomatic infections. More thorough screening will not solve this problem. Rather than finding more patients from whom to expect poor clinical responses, efforts would be better spent studying the cultural factors that impede compliance with the treatment regimens and how clinicians can overcome these factors. As primary physicians of many Cambodians, we are convinced that these cultural beliefs also act as barriers to treating this population's other asymptomatic chronic illnesses like hypertension and hypercholesterolemia.

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REFERENCE

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Radiologic Case

A Young Woman With Vague Lower Abdominal Pain

MARY ELLEN DIRLAN, *Tucson;* JOHN K. CROWE, MD; *and* JONATHAN M. LEVY, MD, *Scottsdale, Arizona*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 22-year-old woman presented with vague lower abdominal pain. After a negative pregnancy test, an x-ray film of the pelvis was taken, and an ultrasound examination was done (Figures 1 and 2).

What is the diagnosis?

What is this patient's prognosis?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION.

Figure 1.—A radiograph of the pelvis shows an area of calcification **(arrow).**

Figure 2.—A pelvic ultrasonogram shows a left adnexal mass behind the uterus **(between markers).**

(Dirlan ME, Crowe JK, Levy JM: A young woman with vague lower abdominal pain. West J Med 1989 Mar; 150:349-350)

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DIAGNOSIS: Benign cystic teratoma (dermoid cyst)

The radiograph of the pelvis (Figure 1) shows a dense calcification with an appearance similar to a tooth in the left side of the pelvis. On the ultrasonogram (Figure 2), a well-circumscribed, echogenic, 6.7-cm mass is seen in the left adnexal region extending behind the uterus. Additional views showed dense acoustic shadowing behind a small echogenic region of the mass. The association of a pelvic mass with a toothlike calcification is essentially pathognomonic of dermoid cyst.

Approximately 15% of ovarian tumors are of germ cell origin, and, of these, 95% to 98% are benign cystic teratomas (dermoid cysts). This tumor consists of well-differentiated tissues derived from ectoderm, mesoderm, and endoderm. It may contain elements of skin, hair, fat, and muscle, as well as bone, cartilage, and teeth. Most investigators believe that this tumor develops parthenogenetically from the basic germ cell because the karyotype is usually that of normal female (46,XX), and no genetic marker has ever been identified in the tumor that was not also present in the host.

Dermoid cysts are unilateral in 80% to 85% of cases, and 75% are 10 cm or smaller. The tumor is usually asymptomatic. As it grows, it may produce local pressure and abdominal discomfort. Menstrual irregularities are uncommon. These tumors are frequently found on a routine physical examination or on abdominal radiographs taken for other reasons. Ultrasonography may be used to differentiate the dermoid cyst from other ovarian lesions by the presence of a tooth; fat-fluid or hair-fluid levels within the cyst; or a highly reflective, irregular solid component (Rokitansky's protuberance) within the wall of the cyst.

Rarely, complications secondary to the tumor may arise and necessitate an emergency operation. The most frequent complication is torsion, occurring in about 10% of patients. This occurs predominantly in young patients and may be associated with infarction or rupture of the tumor. The incidence of rupture is rare (0.7% to 1.3%), and it is usually seen during pregnancy or labor. The intra-abdominal spillage of the tumor contents results in a chemical peritonitis. The resultant granulomatous reaction and formation of dense adhesions to adjacent structures may cause a fistula to form, with drainage into other abdominal organs such as bladder, small bowel, rectum, sigmoid colon, or vagina. Malignant change is rare (less than 0.5%) and occurs during the fifth and sixth decades. The malignant tumor is most often squamous cell carcinoma, although melanomatous and sarcomatous changes have also been reported.

Because dermoid cysts are most commonly found during the reproductive period, treatment is aimed at preserving as much of the normal ovarian tissue as possible. The tumor is therefore resected from the ovary, even though only a small segment of ovary may remain. The prognosis is excellent, and many patients are able to conceive without complication.

Treatment of a secondary malignant tumor arising in a benign cystic teratoma also involves excising the tumor. The prognosis depends on the presence or absence of dissemination. Malignant tumors usually metastasize early. Spread is by direct continuity, peritoneal seeding, or through an invasion of blood vessels. The lymph nodes are generally spared. Overall, the prognosis for a malignant tumor is poor. The results of adjunctive therapy are generally disappointing, although total pelvic irradiation is commonly used postoperatively.

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Health Care Delivery

Patient Evaluations of Low Back Pain Care From Family Physicians and Chiropractors

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We compare health maintenance organization enrollees' evaluations of the care they received from family physicians and chiropractors for low back pain. Patients of chiropractors were three times as likely as patients of family physicians to report that they were very satisfied with the care they received for low back pain (66% versus 22%, respectively). Compared with patients of family physicians, patients of chiropractors were much more likely to have been satisfied with the amount of information they were given, to have perceived that their provider was concerned about them, and to have felt that their provider was comfortable and confident dealing with their problem. Although the more positive evaluations of chiropractors may be related to differences in the patient populations served by the two providers or to benefits of spinal manipulation, it is suggested that a potentially more potent force—the therapeutic effect of the patient and provider interaction itself—may explain the observed differences.

(Cherkin DC, MacCornack FA: Patient evaluations of low back pain care from family physicians and chiropractors. West J Med 1989 Mar; 150:351-355)

Low back pain is a common and costly problem in industrialized societies. Eight of ten adults will experience low back pain at least once in their lifetime,[1] and the annual cost of low back pain to American society in medical care expenses, lost productivity, disability payments, and lawsuits is estimated to be $19 billion.[2]

Although most persons seeking care for low back pain consult doctors of medicine or osteopathy, a large proportion of care is provided by chiropractors. In 1980, 40% of Americans with chronic back problems sought care for their backs from allopathic and osteopathic physicians, while 30% consulted chiropractors.[3] In spite of the important role that chiropractors play in caring for patients with back pain, there is little information in the medical literature about how physicians or chiropractors actually manage patients with back pain or about the relative cost or effectiveness of chiropractic care versus allopathic or osteopathic care for this problem.

We have previously reported that family physicians and chiropractors differ greatly in their beliefs about back pain and in their clinical responses to patients with back pain.[4] In this article we compare patients' evaluations of their care from family physicians and chiropractors.

Methods

Setting

This study was conducted at the Group Health Cooperative of Puget Sound, a 40-year-old staff-model health maintenance organization (HMO) in western Washington State with 320,000 enrollees. Primary care is provided almost entirely by family physicians and pediatricians practicing in 20 medical centers in the Puget Sound area. Enrollees generally have a personal physician from whom they receive their primary care. About 60,000 enrollees younger than 65 years have an insurance benefit that covers up to $200 per year in chiropractic services without requiring a physician referral. Because the HMO does not have chiropractors on staff, chiropractic services are obtained in the community.

Survey Instruments

To gain an initial appreciation of the range of experiences, attitudes, and perceptions of patients with low back pain, we first convened discussion groups consisting of a random sample of the HMO's enrollees who, according to records, had visited a family physician or a chiropractor for low back pain within the previous year. Of the 32 patients asked, 20 agreed to participate in the discussions. While the discussions focused on patients' initial experiences with care from a provider, expectations of the provider, and self-care, patients were encouraged to describe any other aspects of their back care that they thought were important. Proceedings were audiotaped, and transcriptions were reviewed by the investigators. The most notable findings were the importance to many patients of having a provider who conveyed adequate information about their problem, who believed that their pain was real, and who showed concern.

Survey questionnaires were then designed that addressed the main issues identified in the discussion groups, as well as issues that arose in discussions with groups of family physicians and chiropractors.[4] The questionnaires included items about the patient's perceptions of the provider's concern,

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TABLE 1.—*Sample Selection and Response Rate*

Demographic	*Patients of Family Physicians*	*Patients of Chiropractors*
Sampling frame	Enrollees 18-64 years of age who saw a family physician for back problems during April 1-15, 1986, according to appointment logs (n=718)	Enrollees 18-64 years of age with a chiropractic benefit who saw a chiropractor for back problems during April 1-15, 1986, according to billing records (n=348)
Sampling rate and method	50%, simple random sample	100%
Initial sample size, No.	357*	348
Exclusions		
Enrollee claimed visit was not for low back pain, No.	80	87
Enrollee recently disenrolled or died, No.	9	4
Final sample size, No. (%)	268 (100)	257 (100)
Survey results, No. (%)		
Unable to contact	21 (8)	6 (2)
Outright refusal	11 (4)	7 (3)
Other nonresponses	21 (8)	2 (1)
Responded	215 (80)	242 (94)

*Excludes two enrollees who also saw a chiropractor during April 1-15, 1986, and who were asked to complete only the chiropractor questionnaire.

understanding, and skill in providing care for low back pain, the information they were given by the provider, and their satisfaction with the process of care. In addition, patients were asked how many days of restricted activity they had experienced, how satisfied they were with HMO providers for treating problems other than low back pain, and how they rated themselves on a standard four-point health status scale. Questionnaires sent to patients of family physicians and to patients of chiropractors were identical except for response options that were not applicable to both types of providers, such as chiropractors not being asked if they had prescribed drugs since they cannot legally do so. Questionnaires were pretested on a convenience sample of persons who had received care from family physicians or chiropractors for back pain.

Sample Selection and Response Rate

The sampling frame for patients of family physicians consisted of all 718 enrollees between 18 and 64 years of age who, according to appointment logs, had seen any of 181 family physicians at Group Health Cooperative for a back problem between April 1 and April 15 of 1986. A simple random sample of 50% (359) of these patients was chosen to be surveyed (Table 1). The sampling frame for chiropractor patients consisted of all 348 enrollees between the ages of 18 and 64 who had a chiropractic insurance benefit and who, according to billing records, had visited a chiropractor for a back problem between April 1 and April 15 of 1986. All 348 chiropractor patients were surveyed. Two enrollees who appeared in both samples were asked to complete only the chiropractor questionnaire. Children and older adults were excluded to minimize the number of enrollees in the sample with congenital anomalies or low back pain associated with degenerative diseases such as arthritis.

Because the location of enrollees' back pain—low back pain versus mid- or upper back pain, for example—could not be determined from the sampling frames, this was accomplished in the course of the survey conducted during the fall of 1986, about eight months after the visit. Almost a quarter of the enrollees surveyed claimed that their visit in April of 1986 had not been for low back pain (Table 1). Most of these enrollees reported that their pain was in the mid- or upper back, shoulder, hip, or neck. Because the focus of this study was on low back pain, the 80 family physician patients and 87 chiropractor patients who claimed to have experienced some other type of problem were excluded from the study. An additional 13 patients were excluded because they had recently disenrolled or died, leaving 268 family physician patients and 257 chiropractor patients with acknowledged low back pain in the final sample.

After two mailings and repeated efforts to telephone persons not responding by mail, usable responses were received from 215 (80%) of the family physician patients and 242 (94%) of the chiropractor patients (Table 1). Although the rate of outright refusal was similar in the two groups (3% to 4%), patients of family physicians were more likely than patients of chiropractors to have unknown telephone numbers and to claim they had returned completed questionnaires that, in fact, were never received by the study staff.

Presentation of Results and Statistical Tests

Patients were asked to evaluate various aspects of the care they received from family physicians and chiropractors using symmetric five-point Likert scales with response options ranging from very satisfied to very dissatisfied or strongly agree to strongly disagree. Because a skew toward the favorable response categories that is typically found in studies of patient satisfaction was evident in this study, we decided to present the results in terms of the proportions of respondents who were "very satisfied" or who "strongly agreed." The overall results would have been generally the same, though less discriminating because of the ceiling effect, had we incorporated the "satisfied" and "agree" responses into the measures we presented. The χ^2 test was used to test for differences between proportions, and Student's t test was used to compare differences between means. The standard criterion for statistical significance ($\alpha = .05$) was used.

Results

Patient Characteristics

The family physician and chiropractor patient samples were similar in terms of age and sex (Table 2). Although a significantly higher proportion of family physician patients reported fair or poor health status, more than 80% of patients in each group reported good to excellent health. Chiropractor patients reported significantly more episodes of pain and had experienced pain for a longer period of time. Most

patients in both samples had suffered at least five episodes of low back pain or constant pain.

General Satisfaction With Care for Low Back Pain

Even though similar proportions of family physician and chiropractor patients were "very satisfied" with the care they received from Group Health Cooperative providers for problems other than low back pain (40% versus 35%), the percentage of chiropractor patients who were "very satisfied" with the care they received for low back pain was triple that for patients of family physicians (66% versus 22%, $P<.001$).

Satisfaction With Information

Large and consistent differences were found between patients of family physicians and patients of chiropractors in their satisfaction with the information they received about their back problem (Table 3). Patients of family physicians were less satisfied with the information they had received about the cause of their pain and less likely to feel they had received clear information about recovery time and about how to care for their backs after the visit. Family physician patients were also significantly less likely to report having received a graphic description of the causes of low back pain or instruction on exercise, posture, and lifting techniques.

TABLE 2.—*Characteristics of Patients of Family Physicians and Chiropractors*

Characteristic	*Patients of Family Physicians**	*Patients of Chiropractors**
Age, mean years	40.1	41.9
Female, %	48	46
Health status, %†		
Excellent	24	27
Good	57	62
Fair/poor	19	11
Number of pain episodes ever, %†		
1-2	21	8
3-4	13	11
5+	37	64
Constant pain	29	17
Mean years since first pain†	9.3	14.0

*Due to missing information for some items, sample sizes range from 205 to 214 for family physician patients and from 230 to 241 for chiropractor patients.
†$P<.05$.

TABLE 3.—*Patients' Report of Information From Providers**

Patients' Analysis	*Patients of Family Physicians, %†*	*Patients of Chiropractors, %†*
Very satisfied with amount of information provided about the cause of my pain	17	53
Strongly agree that provider gave clear idea about recovery time	16	44
Strongly agree that I knew what to do to take care of my back after the visit	23	51
Provider used model or chart to describe cause of pain	27	80
Provider gave instructions on back exercises	55	76
Provider gave instructions on posture and lifting	47	78

*All comparisons are significant at $P<.05$.
†Sample sizes range from 208 to 215 for family physician patients and from 234 to 240 for chiropractor patients.

Perceptions of Provider Concern

Patients of family physicians and patients of chiropractors also differed notably in their perceptions of their provider's concern. Compared with patients of chiropractors, patients of family physicians were significantly less likely to have been satisfied with the amount of time the provider listened to them, to have felt that their provider believed their pain was real, to have thought their provider understood their concerns about the cause of the pain, and to have believed their provider was concerned about their condition after they left the office (Table 4).

Perceptions of Provider Comfort and Confidence

Patients of the two types of providers were also found to differ greatly in their perceptions of the degree of confidence and comfort their providers brought to their visit for back pain. In contrast to 60% of the chiropractor patients, less than a fourth of the family physician patients strongly agreed that their provider seemed confident and comfortable in diagnosing and treating their low back pain (Table 5). Family physician patients were also significantly less likely than chiropractor patients to claim that they agreed with their provider about the underlying cause of their back pain (57% versus 83%). Most patients who did not indicate agreement with their provider indicated uncertainty rather than actual disagreement.

Perceived Deficiencies of Care

Of the family physician patients, 46%—compared with 15% of the chiropractor patients—believed that there were things their provider did not do that would have been helpful. Of the 96 family physician patients who held this belief, 49%

TABLE 4.—*Patients' Perception of Providers' Concern**

Patients' Perception	*Patients of Family Physicians, %†*	*Patients of Chiropractors, %†*
Amount of time provider spent listening to my description of pain (very satisfied)	28	53
Provider seemed to believe that my pain was real (strongly agree)	38	71
Provider understood my concerns about the cause of my pain (strongly agree)	25	55
Provider's concern about my pain after the office visit (very satisfied)	20	58

*All comparisons are significant at $P<.05$.
†Sample sizes range from 211 to 215 for family physician patients and from 239 to 240 for chiropractor patients.

TABLE 5.—*Patients' Perception of Providers' Confidence and Comfort Managing Low Back Pain**

Patients' Perception	*Patients of Family Physicians, %†*	*Patients of Chiropractors, %†*
Provider seemed confident that the diagnosis s/he gave me was correct (strongly agree)	23	60
Provider seemed confident that the treatment s/he recommended would work (strongly agree)	23	61
Provider seemed comfortable dealing with my back pain (strongly agree)	17	59

*All comparisons are significant at $P<.05$.
†Sample sizes range from 208 to 214 for family physician patients and from 239 to 240 for chiropractor patients.

desired more information (primarily diagnostic tests and specialty consultations) and 39% wanted other therapies (primarily chiropractic manipulation). Patients of family physicians were also significantly less likely than patients of chiropractors to report that they would return to the same provider in the future for low back care (60% versus 87%, respectively). The most frequently cited items that the 35 patients of chiropractors indicated they would have found helpful but did not receive were more information of various types (9 patients), massage (7 patients), physician referral (4 patients), and pain killers (3 patients).

Disability

The number of days patients claimed they had been unable to carry out their normal activities during the approximately eight-month period between the index visit and the survey date was significantly higher for family physician patients (mean 39.7, median 7) than for chiropractor patients (mean 10.8, median 0). Nearly half (48%) of the family physician patients reported that they were restricted for more than a week, compared with 17% of the chiropractor patients.

Controlling for Health Status and Number of Pain Episodes

To determine whether the differences between the reports of the patients of family physicians and chiropractors could be explained by the observed differences in their health status, frequency of back pain episodes, or years since first episode of back pain (Table 2), we repeated the analyses controlling for the effects of these variables. For patients of both family physicians and chiropractors, measures of patient satisfaction were found to be negatively correlated with the number of episodes of back pain the patient had experienced and with health status but not with the number of years since the first episode of back pain. Controlling for these variables did not materially affect the results.

Discussion

Persons who sought care for low back pain from chiropractors rated the care they received much more highly than persons who sought care from family physicians. Patients of chiropractors were more likely than patients of family physicians to have been satisfied with the information they were given about their problem, to have perceived that their provider was concerned about them during and after the visit, and to have felt that their provider was comfortable and confident in managing low back pain. Patients of chiropractors were also more likely to report that they would return to the same provider for care and were less likely to report that there were things the provider did not do for them that would have helped. Patients of chiropractors also reported far fewer days of limited activity due to their back pain.

The only other published study comparing allopathic and chiropractic care for back problems reported similar results. In their study of workers' compensation cases, Kane and co-workers reported that patients who received care for back or spinal problems from chiropractors felt more welcome and were more satisfied with the provider's explanation of their problem and treatment than were patients of allopathic physicians. No differences were found in functional improvement.[5]

There are a number of possible explanations for the differences observed in this study. One is that the family physicians and chiropractors saw different types of patients. From Table 2, we know that although the two patient groups were similar in terms of age and sex, they differed in terms of health status and number of previous episodes of back pain. Controlling for these differences, however, did not materially affect the results. It is not known whether there were differences in socioeconomic status between the two patient populations studied. While one of the earliest reports of chiropractors indicated that they attracted persons from the lower socioeconomic strata,[6] a more recent and nationally representative survey found the likelihood of visiting a chiropractor was not clearly related to either income or educational level.[7]

We do not know why individual patients selected a particular provider or whether patients had different expectations about the ability of each type of provider to help them. We presume that enrollees who chose to see chiropractors did so because of an expectation that their needs were more likely to be met by a chiropractor than by a family physician. But what about enrollees who chose to see a family physician even though their insurance covered chiropractic services? One would expect the 54 enrollees in this group to have been more satisfied with their care from family physicians than were enrollees whose only option in terms of insurance coverage was to see a family physician. In fact, we found the responses of the enrollees in these two groups to be virtually identical. This suggests that the more favorable views about chiropractors do not merely reflect the benefits of being able to select the type of provider that one expects to be the most helpful.

Practice setting differences, with the family physicians being on salary within a single HMO and the chiropractors in fee-for-service practices, could also have influenced the findings. A fee-for-service practice provides different incentives than a salaried practice in an HMO for scheduling return visits, ordering tests, referring patients to specialists, and possibly for length of visit. In addition, therapeutic options such as physical therapy may be more readily available within an HMO system than they are in most fee-for-service practices. Nevertheless, family physicians in fee-for-service practice and in HMOs have been shown to have generally similar beliefs and behaviors related to the management of low back pain.[4] Hence, it is unlikely that practice setting differences alone are responsible for the large differences that were observed between family physicians and chiropractors.

The differences in patients' evaluations of their care from family physicians and chiropractors may have resulted from differences in the providers themselves. Differences between the types of persons who ultimately enter chiropractic and medicine are evident even before they begin training. Compared with other health professionals, chiropractors are more likely to have chosen their profession after having witnessed a miraculous success achieved by a member of their profession[8] and to have chosen their profession as a second career.[9] Chiropractors are also more likely than physicians to resemble their patients socioeconomically and are less oriented toward financial success than are physicians.[8]

Probably the most profound difference between chiropractors and family physicians is their training and consequent beliefs, attitudes, and behaviors concerning the management of low back pain. Chiropractic training focuses on the spine and emphasizes a particular therapeutic tech-

nique—spinal manipulation—while family physician training covers the entire spectrum of clinical topics and does not emphasize the paramount importance of a particular therapy, even for back pain. Chiropractors generally believe that most back pain is caused by anatomic derangements in the spine, such as vertebral subluxations, that can be identified on a spinal radiograph and effectively treated using spinal manipulation. In contrast, family physicians believe that most back pain is caused by muscle strain, that spinal radiographs are rarely useful, that appropriate therapy does not depend on a precise diagnosis, and that patients will get better without professional help.[4] These differences may explain why family physicians are more likely than chiropractors to feel frustrated by back pain patients, less likely to think they can help prevent future episodes of back pain, and less confident that their back pain patients are satisfied with their care.[4] The results of this study suggest that patients may be more satisfied with the confident and definite approach of chiropractors than with the less certain and more scientific approach of family physicians. Other factors, such as possibly longer visits with chiropractors than with family physicians, could also explain differences in patient satisfaction.

There are many differences between family physicians and chiropractors that could explain the observed differences in patient satisfaction, and it is not possible from this study to determine with certainty which might be the most important. The most clinically relevant question for patients and physicians, however, is whether patients' more positive evaluations of chiropractors result from specific benefits of spinal manipulation or from other aspects of the interaction between patient and provider. Although studies of spinal manipulation for back pain have generally found that it provides more immediate relief of back pain than other methods with which it has been compared,[10,11] other differences between the chiropractic and medical approach to low back pain could conceivably have a more potent effect on patient outcomes.

Coulehan claims that an interaction with a patient may have either a "beneficial (positive placebo) or harmful (negative placebo) influence on the patients' condition," and that "in many cases inadequacy of the medical process for musculoskeletal pain causes continuation of symptoms which then might be relieved through certain positive features of the chiropractic process." He suggests that chiropractors may be better able than allopathic physicians to promote patient acceptance and validation, fulfill expectations, provide explanations, and engage patients' commitment because chiropractors strongly believe their therapy will help and they are less constrained by "scientific" models of disease.[11]

Recent studies have shown the importance of the patient-provider interaction on the outcomes of care. For example, in a study of the outcomes of new episodes of common nonrespiratory tract symptoms, Bass found that the only element in the process of care that was related to early resolution of a patient's symptom was agreement between physician and patient about the nature of the problem.[12] In a randomized study of patients with symptoms but no abnormal physical signs and in whom no definite diagnosis was made, Thomas reported that patients given a firm diagnosis and assurance that they would be better in a few days were more satisfied and were more likely to get better than patients whose physician expressed uncertainty about the diagnosis and the likelihood that the therapy would be effective.[13] Other studies of the therapeutic aspects of the clinical encounter have been summarized by Novack.[14]

Summary

The science of medicine may not provide physicians with tools that are generally effective for managing back pain. Although particular therapies, such as spinal manipulation, may in fact be effective for some patients, there is reason to think that other aspects of the patient-provider interaction may have a greater influence on the outcome of care. Greater consideration should be given to the potential for the art of medicine to provide low back pain patients with effective therapy.

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Physician Communication Skills and Malpractice Claims

A Complex Relationship

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We assessed the relationship between patients' opinions about their physicians' communication skills and the physician's history of medical malpractice claims. The sample consisted of 107 physicians and 2,030 of their patients who had had an operation or a delivery. Although patients tended to give their physicians favorable ratings, they were least satisfied with the amount of explanations they received. Patients gave higher ratings to general surgeons and obstetrician-gynecologists and poorer ratings to orthopedists and anesthesiologists. Women and better-educated patients gave higher ratings on explanations and communication to physicians with fewer claims. Men and patients with less education, however, gave higher ratings on these dimensions to physicians with more claims. These findings suggest the need for physicians to tailor their communications to a patient's individual needs. Improved communication between physicians and patients may result in fewer nonmeritorious malpractice claims while leading to less costly resolution of meritorious claims.

(Adamson TE, Tschann JM, Gullion DS, et al: Physician communication skills and malpractice claims—A complex relationship. West J Med 1989 Mar; 150:356-360)

Communication between physician and patient is a topic of increasing interest to the medical community, possibly because of legal developments in recent years. On the one hand, patients' interests are now protected by informed consent statutes that have been enacted in many states. These statutes require physicians to convey adequate information about medical procedures. On the other hand, the cost of malpractice claims in the United States has risen dramatically in recent years.[1] Some investigators have theorized that poor communication between physicians and their patients may be a major cause of malpractice claims.[2-4] Although the relationship between malpractice claims and physician communication skills has not been assessed directly, there are several sources of evidence that suggest such a relationship.

Physician communication skills have been reported to be generally inadequate. In a review of physician-patient communication research, Waitzkin concluded that patients usually want more information than their physicians provide. He pointed out that physicians may fail to address patients' concerns fully by discouraging questions, interrupting, and focusing on medical history-taking.[5] Similarly, Faden and associates found that patients preferred far more detailed disclosures, especially about risks and alternative therapy, than were routinely offered.[6] Gardner reported that the most frequently cited reasons for malpractice actions were patients' unhappiness with their underlying disease and a lack of communication resulting in patients' failure to anticipate either their level of pain or the cost of medical care.[7] These researchers concluded that the key to preventing malpractice claims lies in honest, open communication at all times, especially when the outcome of treatment is not successful.

In this study we examine the relationship between the number of malpractice claims filed and patients' assessments of their physicians' communication skills. We expected to find that a greater number of malpractice claims would be associated with more negative patient opinions when controlling for number of years in practice.

Physician and patient characteristics were also thought to have a potential effect on this relationship. For physicians, specialty was targeted as an important variable, since the rate of malpractice claims changes according to specialty.[8] For patients, demographic characteristics were considered important because they have been related to satisfaction with medical care in numerous studies. Older, better-educated female patients are generally more satisfied than younger, less-educated male patients.[9]

Based on the above considerations, we expected that physician specialty, along with number of claims, would be related to patients' opinions about physicians' communication skills. Further, we hypothesized that patient demographic characteristics, along with malpractice claims, would be related to their assessment of physicians' communication skills.

Methods

The research was conducted jointly by the Cooperative of American Physicians/Mutual Protection Trust, a physician-owned interindemnity trust, and the Professional Compe-

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tence Assurance Program. The latter is a continuing medical education program that features an educational intervention based on individual physicians' needs.[10,11]

Physician Selection

All potential participants were members of the Cooperative of American Physicians (CAP). They included surgeons, obstetrician-gynecologists, anesthesiologists, and primary care physicians. They practiced in all geographic areas of California. To assure a range in numbers of malpractice claims, recruitment was stratified initially to include both physicians with no claims or one claim during the time they had been CAP members and those with multiple claims. Later, claims received before membership in CAP were added. Each physician was sent a personalized letter by Professional Competence Assurance Program's medical director, along with a letter of endorsement by CAP's educational director. Invitations were sent to 416 members; 107 (26%) agreed to participate.

Patient Selection and Survey Administration

Participating physicians or their office staff were asked to select 30 patients who had had a surgical procedure or a delivery during the previous year and were in hospital for at least one day. They were instructed to use a consecutive listing of patients derived from the appointment schedule or the computer billing system. Patients were eligible only if they were adults who could read and write English.

The study was designed to be as unintrusive as possible. Also, patient confidentiality was preserved by having the surveys mailed directly from the physician to his or her patients. Surveys were sent with a cover letter on the physician's stationery that explained the project and requested that patients complete the surveys and return them, unsigned, to the Professional Competence Assurance Program's office. A reminder postcard was sent to the patients about two weeks after the surveys were mailed.

Physician Sample

The final sample of 107 physicians included 19 general surgeons, 31 orthopedic surgeons, 28 obstetrician-gynecologists, 16 anesthesiologists, 5 primary care physicians, and 8 other surgeons—urologic, plastic, vascular, and neurologic. The average age of participating physicians was 51 years. All were men except for one general surgeon. They had been in practice an average of 19 years. The mean number of total claims, meritorious or not, since beginning practice was 4.45. Fewer physicians (68%) with multiple claims declined the invitation to participate than those who had either no claims or one claim (77%). Participation rates were similar among the surgical subspecialties (ranging from 26% to 29%) but were lower for anesthesiologists (12%).

Patient Sample

Surveys were obtained from 2,030 patients (a response rate of 68%). Of surveys received, 94 (5%) were discarded because they were filled out incorrectly or were missing data. The response rate was similar (65% to 67%) among the surgical subspecialties but was lower among the anesthesiologists (56%). The response rate for patients of physicians with fewer claims was 69%, and that for patients of physicians with multiple claims was 61%. Of all patients, 59% were women, their average age was 51 years, and their average years of education was 13.75.

Patient Survey

Patients' opinions of their relationship with their physicians were assessed by means of a survey developed for this project. Items from other surveys were used or adapted when appropriate. These included assessments of how well the physician communicated, the thoroughness of treatment or examinations, whether the patient's concerns were taken seriously enough, and the accessibility of the physician.[12,13] Items were added to measure the adequacy of informed consent and the helpfulness of the physician's office staff. The survey also included items regarding information or services patients might have wanted. These "patient-need" items were meant to provide an indirect measure of negative patient opinion.

Except for the patient-need items, all items measuring patients' opinions were worded as statements to which the patient could respond on a six-point scale, from "strongly agree" to "strongly disagree." Half the items were positively worded, and half were negatively worded. The patient-need items were scored "yes" or "no." The content and length of the survey varied according to specialty.

The survey for patients of surgeons contained 62 items; obstetrician-gynecologists, 74 items; and primary care physicians, 68 items. The anesthesiologists' survey omitted items relating to accessibility of the physician, helpfulness of office assistants, and items relating to rapport. Seven items specific to anesthesia were added, for a total of 28 items, 21 of which also appeared on the other surveys.

Patient Opinion Scales

The 52 opinion items common to all but the anesthesia survey were subjected to a factor analysis. Patient-level data were used. Six factors accounting for 61% of the variance were obtained. Six scales based on the factors were constructed. Means of available items were used so that anesthesiologists were not penalized by having fewer items. Scales were scored from 0 to 100 and were named to reflect the items of which they were composed: Understanding and Empathy, Competence, Accessibility of Physician, Helpfulness of Office Assistants, Explanations, and Absence of Communication Problems. A seventh scale, Patient Need for Services and Information, was constructed using the mean of the patient-need items.

Statistical Analyses

Physician-level data were used in all analyses. Four series of analyses were done: a set of analyses of covariance and three sets of repeated measures of analyses of covariance. Years in practice was the covariant in all analyses. The dependent variables in each set of analyses were the seven patient-opinion scales. The first set of analyses used claims and specialty as the predictors, the second used claims as predictor and patient sex as the repeated measure, the third used claims as predictor and age as the repeated measure, and the fourth used claims as predictor and education as the repeated measure.

To use patient-level demographic information at the physician level, each demographic variable was converted into a dichotomous variable. To compare the opinion scores of patients with different demographic characteristics, using the physician as the unit of analysis, it was necessary to compute mean scores for physicians at each level of a given demographic variable. Demographic variables that were contin-

uous at the patient level could not be retained as such at the physician level because for many values (levels)—age, for example—there would be few cases. Patient education and age, therefore, were converted to dichotomous variables, although a three-way split may also have been possible.

Patient age was divided into younger (<45 years) and older (≥45 years). Similarly, patient education was divided into less educated (≤12 years) and more educated (>12 years). For each level of a demographic variable, physicians received a score that was the mean opinion score of patients in that demographic group. Because physicians had two scores for each demographic variable, these were within-physician variables and were treated as repeated measures in the major analyses.

Number of claims also was converted to a dichotomous variable by means of a median split (fewer [N = 58] means three or fewer claims; more [N = 59] means more than three claims) so that interactions between claims and the demographic variables could be computed.

The number of physicians in the primary care and other surgical specialties was low, so that these specialties were deleted in any analyses using specialty as a predictor (number lost = 13). Additionally, obstetrician-gynecologists had only women patients, necessitating the deletion of that specialty from any analyses using patient sex as a variable (number lost = 28).

Results

Descriptive Information from Patient Survey

The patients' overall opinions of their physicians were relatively high, with only 15 items receiving an average rating below 80 out of a possible score of 100. Physicians' scores were above an average of 20 on seven need items; that is, more than 20% of patients expressed a need for these services. Items with low patient-opinion scores and high patient-need scores are shown in Table 1. Many of these items concerned the patients' desire for more information, such as costs of procedures, drug side effects, or postoperative recovery.

Major Analyses

Claims and specialty as predictors. The number of claims was not significant in any of the analyses, nor was the interaction between claims and specialty. Specialty was a significant predictor of patient opinion in four of seven analyses: for Understanding and Empathy ($f[3, 85] = 13.34, P < .001$), Helpfulness of Office Assistants ($f[2, 71] = 4.13, P < .03$), Explanations ($f[3, 85] = 3.21, P < .03$), and Absence of Communication Problems ($f[3, 85] = 7.70, P < .001$). Table 2 shows the mean of each specialty on all patient-opinion scales, adjusted for number of years in practice. The means of specialties that were significantly different are indicated. The overall mean on the Explanations scale was below 80, suggesting that this was an area that generally needed improvement. General surgeons had significantly higher mean scores than other specialists on most scales, and anesthesiologists or orthopedists generally had lower mean scores. Obstetrician-gynecologists fell between—usually closer to the level of the general surgeons.

Claims and patient sex as predictors. No significant main effects were found. Two significant interaction effects were obtained between number of claims and patient sex. These were for Explanations ($f[1, 76] = 4.80, P < .04$) and Absence of Communication Problems ($f[1, 76] = 4.15, P < .05$). The interactions are shown in Figure 1. The pattern of interactions for these two patient-opinion scales is similar. Female patients of physicians with fewer claims and male patients of physicians with more claims tended to be more satisfied with their physicians' explanations and communication style.

Claims and patient age as predictors. One significant main effect was obtained for age, for Patient Need for Services and Information ($f[1, 99] = 5.33, P < .03$). Younger patients wanted more services and information (mean = 23.40) than did older patients (mean = 15.84). There were no other significant effects.

Claims and patient education as predictors. No significant main effects were found. Two significant interactions between number of claims and education were obtained, for Explanations ($f[1, 103] = 5.12, P < .03$) and for Absence of Communication Problems ($f[1, 103] = 5.41, P < .03$). Figure 1 shows the interaction effects. The interaction effects between claims and education are for the same scales as the interaction effects between claims and sex. The pattern of effects is parallel, with men and less-educated patients evaluating physicians similarly and women and more-educated patients evaluating physicians similarly.

Discussion

It has long been speculated that poor communication between physicians and patients is the basis for many malpractice claims, meritorious or not. The results of this study suggest that a relationship does exist between patient opin-

TABLE 1.—*Patient Perception of Medical Care*

Opinion Items With Lowest Rankings	*Mean Score**
Cost of procedure was as expected	49
Patient told enough about drug side effects	51
Pain after the procedure was as expected	61
Patient told enough about condition	66
Preferred to wait for own physician rather than see on-call physician	67
Patient was comfortable asking advice about sex (Obstetrics only)	71
Patient willing to phone physician about problems	73
Patient usually seen in office within 15 minutes	73
Referring physician and this physician seemed to be in contact	73
Late appointments were always explained	74
Complications after surgical procedure were not unexpected	76
Physician took time to tell patients how they are doing	77
Patient knew whether to see referring physician or this physician	77
Patient told about alternate treatment	78
Patient told enough about how drug prescribed helps condition	78
Need Items With Highest Rankings	*Patients, %*
Patient would like reading materials about condition	33
Patient would like counseling about diet	23
Patient would like information about prescribed medications	22
Patient would like information about health and life-style	21
Patient would like information about own anatomy and physiology (Obstetrics only)	21
Patient would like counseling about condition	21
Patient would like to learn about breast self-examination (Obstetrics only)	21

*A six-point scale was used, with the scales scored from 0 to 100.

TABLE 2.—*Mean Scores of Each Specialty on Patient Satisfaction Scales**

Specialty	Scale: Understanding	Competence	Access	Office Staff	Explanation	Communication	Needs
General surgery	88†	92	89	88†	70†	86†	18
Orthopedics	84	88	83	82‡	64‡	84	19
Obstetrics-Gynecology	85†	90	87	85	69†	89†	21
Anesthesia	76‡	90	..	..	65	81‡	21

*A six-point scale was used, with the scales scored from 0 to 100.
†Mean score of this specialty is significantly higher.
‡Mean score of this specialty is significantly lower.

ions of physician communication and physicians' history of malpractice claims. This relationship, however, is complex: female patients and more highly educated patients evaluate their physicians in the hypothesized direction. That is, they are more satisfied with physicians who have fewer claims. In contrast, male patients and less educated patients are more satisfied with physicians who have more claims. These differences were found for two of the seven scales that were examined: Explanations and Absence of Communication Problems. Physicians' scores on Explanations were consistently lower than on the other scales, suggesting that patients are less satisfied with the information they receive about their condition than with any other area of communication with their physicians. General surgeons and obstetrician-gynecologists also receive higher patient-opinion ratings than orthopedists and anesthesiologists.

The ability to generalize about these findings is limited because of several methodologic considerations. First, the identification of patients was delegated to physicians' office staffs. The importance of selecting a consecutive sample of patients was stressed to office staff so that any bias in the sample towards more-satisfied patients would be diminished. Second, the physician response to the invitation to participate was 26%. Although this response rate is not ideal, it is reasonable for this type of study. Nonrespondents tended to have fewer claims and apparently did not think participation would be useful. The patients' response rate of 68% is similar to that obtained in another study using a mailed survey; that study also found that nonrespondents were more satisfied with their care.[14] Thus, the sample bias in this study is probably towards more dissatisfied patients. Third, this study does not distinguish between open and closed claims since a significant proportion of the claims had not been settled and since we were more interested in characteristics that lead patients to file a claim, meritorious or not.

Our finding of a relationship between sex and physicians' malpractice history for the Explanation and Communications scales can be only partially explained. If physicians with fewer claims are better communicators than those with more claims, then female patients and patients with more education may have been sensitive to this and, therefore, may have given better scores to physicians with fewer claims. There is evidence to support this speculation. Resident physicians give more explanations to female patients than to male patients and to better educated patients than to those who are less educated.[5,15] The finding that men and less-educated patients prefer physicians who have more claims might be explained by a tendency for these patients to favor a more authoritarian, dependent relationship with their physicians.

Length of contact is another important issue in physician-patient communications. Whereas women patients often have seen their obstetrician-gynecologists for many years, patients usually meet their anesthesiologists the day before an operation. This brief duration of contact may ex-

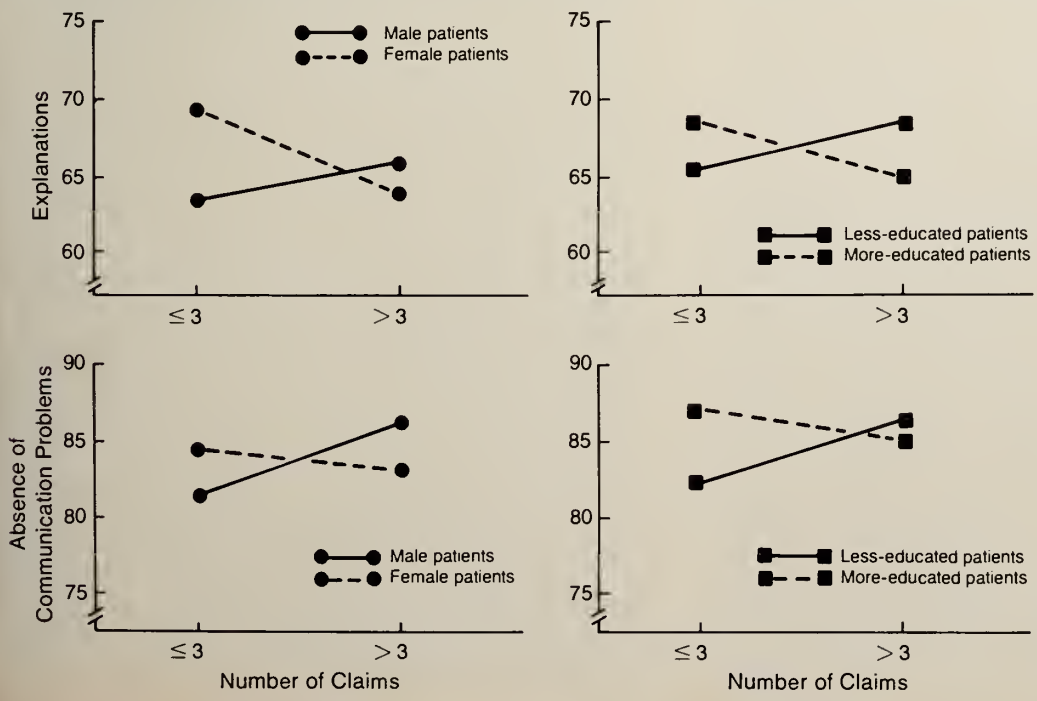

Figure 1.—Patient opinion scores are shown for physicians with few or many malpractice claims, by patient sex and education.

plain the low scores obtained by anesthesiologists in comparison with other specialists. These physicians may need to learn to develop rapport quickly with a patient in the stressful preoperative situation, especially with the advent of more ambulatory surgical treatment.

Another important finding of this study was that the mean score of the Explanation scale was 20 points lower than that of the other scales. This suggests that physicians do not adequately explain aspects of care related to the nature of procedures, their risks, complications, cost, or postoperative discomfort. These findings are consistent with reports by other investigators.[5-7] A lack of adequate information may cause patients to have unrealistic expectations about outcomes; when these expectations are unmet, patients may be more likely to file a malpractice claim. Case law over the past 20 years requires that patients be instructed about procedures and assumes that patients understand what they have been told.[16] Adequately informing patients about their conditions may facilitate forming realistic expectations concerning the outcomes of medical care. Previous research has suggested that more complete preoperative explanations could decrease morbidity, medication use, and length of hospital stay.[17,18] An additional solution would be to educate the public to ask their physicians more questions. This was done with a group of hypertensive patients, resulting both in more communication and a reduction in blood pressure levels when compared with a control group.[19] Patients who speak more during office visits are also more satisfied with their physicians.[20]

Our findings have educational implications for practicing physicians and their professional liability carriers. Physicians must learn to adapt their communication styles to the individual variations in their patients' intellectual and emotional needs. When a patient prefers less explanation, care must be taken to see that adequate informed consent is given. In this study, the inverse perceptions reported by male and female patients and more- and less-educated patients about physicians with few and many claims reinforces the importance of this. McCaughrin also stresses that standard messages cannot be given to all patients.[16]

Our study, which explores the application of survey methods in the area of malpractice claims, is an initial step toward understanding the complicated interplay of communication between physicians and patients, patient satisfaction, and malpractice claims.

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Information

Organ Transplants

A Search for Health Policy at the State Level

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UNTIL THE FALL OF 1987, Oregonians' interest in the issue of public financing of organ transplants ranked well below their concern for the infestation of the Gypsy moth in our forests. As it became obvious, however, that actual lives were being prematurely lost as a result of a lack of state funding for specific medical procedures, public interest rose precipitously. Wide awareness of the issue began as the media vibrated to the fate of 7-year-old Adam Jacoby ("Coby") Howard, a leukemia patient who needed a bone marrow transplant to survive. He was the child of a single parent on Medicaid and ineligible for government funding. Telephones to legislators buzzed and the public outcry grew while some charitable souls passed the hat in the hope of raising $70,000 in time to save the lad. He died last winter, but the issue lives on to haunt Oregonians and their legislative representatives, as it will, in all probability, eventually haunt the nation and Congress. How to pay for expensive high-technology medical services to the poor presents a grave and undeniable contradiction to our tradition of all for everyone. Like it or not, Oregon has become the first state in the union to meet the problem of health rationing head on with a deliberate policy decision.

The Oregon legislature has a particularly swift and open accountability to the public for how it spends public money because the tax base is limited. Without a sales tax, present state income is desultory as the nation slowly recovers from the national recession of 1981 to 1985. The state constitution forbids bonded indebtedness for public services. The recondite issue of organ transplants passed over the 1987 legislature in a health budget that provided few increases in services for the medically indigent while eliminating the provision to finance organ transplants—with the exception of corneal and kidney transplants. These were left in the bill because corneal transplants represent a relatively infinitesimal amount of money and kidney transplants are reimbursed under a federal program. Neither offered any strain to a slim state budget. In the final days of the 1987 session, with the legislators largely unaware of the implicit life-and-death issue and without open legislative exploration and debate, financing of heart, liver, lung, and bone marrow transplants was eliminated, effective July 17, 1987.

When Coby Howard's family discovered his plight of needing $70,000 before the regional hospital would do a bone marrow transplant, they appealed to state authorities for dispensation of the recent legal restrictions. What followed is characterized by the family as a "frightful runaround." Differing and conflicting decisions were handed down by various levels of the administration, finally ending as a blanket refusal to fund the indicated treatment.

The family next appealed to the Oregon State Emergency Board, made up of legislators empowered to alter the budget during the legislature's interim. This body started the biennium with $25 million, but by the time the issue of funding organ transplants was brought before them, they had already spent $17 million meeting an unplanned expense of a plague of forest fires. Understandably, they were most anxious to make the best possible use of the remaining funds and, in considering the plea for organ transplants, they also had to consider a plea from another medically neglected portion of the population—poor pregnant mothers and their children. Prenatal services in Oregon for the poor had completely evaporated so that the only medical help a poor pregnant Oregonian could expect was admission to hospital to deliver *after* she proved she was in labor. Consequently, the issue before the Emergency Board became framed as "all or nothing"—whether the limited state funds would be used for a few persons needing organ transplants or for many others, including approximately 2,200 poor pregnant women. The decision was anything but a decision by default, for the Emergency Board carefully considered and heatedly debated what to do, finally going for "other" services by one vote.

Coby Howard's family then went public in an attempt to raise medical funds directly. Torn with mixed feelings, they turned the dying child into a publicity event and his smiling, wan face became familiar on local television screens. They raised but $30,000 of the necessary $70,000 before he died without benefit of an accepted medical treatment.

In another part of the state, centering on the city of Bend, which boasts of a much stronger sense of community than the metropolitan Portland area Coby had called home, a similar drama unfolded. There, a 17-year-old boy with a similar disease also became a publicity event, but here the prerequisite $70,000 was raised by numerous, intense charity events. This lad is now alive. Success in the Bend area quickly turned to chagrin with the state's epidemiologist's prediction that 34 medically poor persons could be expected to need organ transplants before the legislature met again in 1989.

Continuing reaction to the issue has varied. Like most news, the transplant issue had a two-month life span before television and newspaper coverage turned to police scandals, local teenaged gang warfare, and more global violence. The issue has never been lost to the public or the legislature, however. The inhumanity of an "all or none" policy decision on organ transplants, for recipients and decision makers alike, was clear to the Emergency Board. One of the most reasonable arguments put forth by those seeking transplant funding was the arbitrary and unreasonable deletion of funds for a particular treatment—organ transplants—when other "questionable" treatments such as coronary bypass operations consume considerably more state funds. The Emergency Board, anticipating that the issue will reappear in the 1989 legislative session, recommended that the Interim Committee on Human Services begin a search for a reason-

(Crawshaw R, Garland M, Hines B: Organ transplants—A search for health policy at the state level. West J Med 1989 Mar; 150:361-363)

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able resolution of the issue. In turn, that committee appointed a subcommittee to study the issue for long-term solutions.

One stopgap measure provided by the Emergency Board was the creation of a state trust fund that could accept donations from the public for funding organ transplants for the medically indigent. The fund was intended to secure 62% Medicaid matching funds for any donation. Unfortunately, the fund did not find much support and never met the criterion for implementation of at least $70,000. Subsequently, the federal Health Care Financing Administration has ruled that anything short of "similar treatment of similarly situated individuals as required by . . . the Consolidated Omnibus Budget Reconciliations Act of 1985" would not be matched with federal funds. The Emergency Board's trust fund has since been eliminated. The charitable approach appears bankrupt.

Other reactions to the implicit moral crisis of allowing citizens to die without benefit of full medical support have followed. In response to the uproar in the Bend area, the local state representative asked Oregon Health Decisions to hold an open forum on the problem of health priorities for the state. Oregon Health Decisions is a citizen network dedicated to promoting education and action on the ethical issues in health care in the belief that the health care system should reflect the values of an informed community. The aim of this and subsequent forums across the state was to develop an informed citizenry, all pointed towards a People's Health Care Parliament, for considered citizen influence on the 1989 state legislature on health priorities for the 1990s.

The first open forum was held on a February 1988 weekend in Bend, and, along with the specific issue of funding organ transplants, the broader implications of health care financing were addressed at three different levels. Those present were assigned to small groups charged with developing a consensus on these issues:

- What portion of the general budget should be assigned to health care?
- What portion of the health budget should be assigned to specific populations (infants, children, adults, and the elderly) and what portion should be assigned to specific health care approaches (acute care, long-term care, chronic care, and prevention)?
- What is the specific preference regarding state funding of organ transplants?

The consensus of each group was reported to all present and then, following an open debate, a consensus for the town-hall meeting arrived at. These findings were brought to the People's Health Care Parliament in September, where the process of small group discussions followed by open consideration and full debate by the 50 representatives from across the state established 15 principles of citizens' values in determining the priorities for health care in Oregon (Table 1). These principles have the attention of legislators and public administrators, so much so that the Oregon Department of Human Services postponed developing its 1989 budget until it received a report from the Parliament.

As for the organ transplant issue, early soundings across the state indicate a low priority in the public's mind. Preliminary findings are that 15% are for state-funded organ transplants, 45% are against, and 40% remain undecided. The predominant wish seems to be for a definitive shift away from funding curative medicine to funding preventive services, a move reflected in the Emergency Board's decision to fund other services, including prenatal care for indigent mothers and their children. The strongest public expression seems to be for defining and guaranteeing a basic health package for all citizens. Definitive findings await the effect of the Parliament on the next legislative session, however.

The serious problem of allocating of state health funds has also been addressed by other state policy bodies. The Oregon Health Council established basic standards from which some procedures were excluded. Intense debate over each exclusion ended with all excluded procedures being retained, however. The Governor's Task Force on Health Care to the Medically Needy also addressed the problem of health care allocation and surfaced with a number of recommendations, including a proposed 1% tax on all providers to be used in underwriting the cost of care for the 20% of the

TABLE 1.—*Principles for Securing Quality of Life in Allocating Health Care Services**

Purpose of Health Services

The responsibility of government in providing health care resources is to improve the overall quality of life of people by acting within the limits of available financial and other resources.

Overall quality of life is the result of many factors, health being only one of these. Others include economic, political, cultural, environmental, aesthetic, and spiritual aspects of life.

Health-related quality of life includes physical, mental, social, cognitive, and self-care functions, as well as a perception of pain and a sense of well-being.

Allocations for health care have a claim on government resources only to the extent that no alternative use of these resources would produce a greater increase in overall quality of life of the people.

Health care activities should be undertaken to increase the length of life or the health-related quality of life during one's life span, or both.

Quality of life should be one of the ethical standards when allocating health care resources involving insurance and government funds.

Why Priorities Need to Be Set

Every person is entitled to adequate health care.

It is necessary to set priorities in health care so long as health care demands and needs exceed society's capacity, or willingness, to pay for them. Thus an "adequate" level of care may be something less than an "optimal" level of care.

How to Set Priorities

Setting priorities and allocating resources to health care should be done explicitly and openly, taking careful account of the values of the broad spectrum of the Oregon population. Value judgments should be obtained in such a way that the need and concerns of minority populations are not undervalued.

Both efficiency and equity should be considered in allocating health care services. Efficiency means the greatest amount of appropriate and effective health care benefits for the greatest number of persons is provided with a given amount of money. Equity means that all persons have an equal opportunity to receive available health services.

Allocation of health care resources should be based, in part, on a scale of public attitudes that quantifies the trade-off between length of life and quality of life.

In general a high priority health care activity is one where the personal and social health benefits-to-cost ratio is high.

Who Sets What Priorities

The values of the general public should guide planning decisions that affect the allocation of health services resources. As a rule, choices among alternative treatments should be made by the patient, in consultation with the health care provider.

Planning or policy decisions in health care should rest on value judgments made by the general public and those who represent the public and on factual judgment made by appropriate experts.

Private decision makers, including third party payers and health care providers, have a responsibility to oversee the allocation of health care resources to assure that their use is consistent with the values of the general public.

*From the September 1988 meeting of the Oregon People's Health Care Parliament.

population without access to health care. This recommendation remains improbable because it not only lacks the governor's strong support, but such a tax focuses on the medical providers. The effect would be little more than another form of cost shifting, failing to place the burden of care on a broad citizen base while begging the moral question of who shall and who shall not receive limited health care resources. Yet another group is reviving an old proposal to form a State Health Plan, a statewide preferred provider organization that would pool the state's employee health fund with the funds for care of the indigent as a base that would insure full health care for all enrollees. The actuarial shortfall of this plan runs approximately $500 million, no small sum in Oregon, and is unlikely to be recovered by economies of scale resulting from making an inefficient health delivery system efficient.

Action is necessary at a number of different levels, and the first is to recognize, as the death of Coby Howard indelibly records, that the supply of health care resources is limited. Neither the public nor the individual practitioner wishes to learn how much sacrifice lies ahead in accepting that the infinite demand for health care has at last reached the limit of willing supply. It is a difficult area for public discourse. It took little time for some ambitious legislators to appear on Oregon television decrying the Emergency Board's decision, ". . . when we are subsidizing 4-H projects at the state fair to the tune of millions yet allowing children to die for the lack of proper care." Of course, as with all demagoguery, this has a kernel of truth but misses, perhaps purposely, the public's need to know what the limits are. The discourse panders to the public with demagoguery that thoughtful legislators and concerned providers are little more than greedy, thoughtless, and inhumane manipulators of a decrepit system.

Nor on another level can the federal government be expected to fund transplants, the artificial heart, and an assortment of other high-technology procedures as it funded kidney transplants in the 1970s. Congress is just as vulnerable as state legislatures when making hard decisions and needs assurances that the public understands that what is called for are wise decisions in the face of an infinite need for health care services. The lawmakers of the land, at all levels, should be encouraged to consider a systems approach to the problems resulting from the fortunate miracles of medical research. Legislators need to address the process of evaluation with a new profundity.

The policy challenge of equitable introduction and delivery of medical innovations calls for a new and higher level of education of the public and its legislators to alternatives that exist within our health care system. The commercialization of health care delivery has done nothing to solve the underlying policy decision of the public's responsibility for the care of the medically indigent. The effect of corporate thinking on medical delivery has made the system more efficient, partially at the expense of those who no longer can enter it. Business cannot be expected to offer solutions to a national moral problem evolving from our inequitable health care delivery system. More is not the answer as the question becomes, more for whom? The goal of business and industry is not to produce morals but profits, which are only moral or immoral in the context of a larger public good.

Nor is it enough to have an "expert" delineate an innovative plan for treating the acquired immunodeficiency syndrome or operating on occluded arteries. Worthy as these plans may be, the public, in the form of government, has become responsible for paying for them with tax funds from a limited budget. The role of the expert is clear and necessary in describing what is possible, but the expert cannot and should not be expected to present the limiting, broad policy values that inform a just democracy. Only legislatures, supported by a courageous constituency, can establish the moral yardstick that must decide which "life and death" health benefits should be pursued under existing circumstances.

Working at the local and state level, Oregon Health Decisions is but one effort in educating the public to their considered expression of human values in the life-and-death decisions of modern medicine. Yet their effort has resonated across the nation. In other states similar citizen responses to the public's responsibility have been initiated, and in October the first meeting of a national organization, American Health Decisions, was held in Denver. The debate needs to be carried from the local level, from the bedside, and across the states to the halls of Congress so that we can establish a new moral tradition, a 21st-century approach, to our responsibility for all the needs of the sick and disabled.

One historic life-and-death national policy should be kept in mind as the debate about health care rationing develops—Selective Service. The American public has a proved ability of fairly deciding who will live and who will die. After failing miserably in 1863 with what ended up as the draft riots, we have accomplished those decisions during four wars. Selective Service worked practically and morally for four elementary reasons. First, the public was convinced that decisions had to be made; volunteering would no longer supply enough personnel to the armed forces to save our country. Second, the rules applied for all. Third, the results were public and open to appeal. Fourth, and especially pertinent to medical rationing, specific decisions were made locally by responsible and accountable citizens who could properly evaluate a particular case against local circumstances.

Remembering that we are strong people, we need leadership with the vision to show us clearly what our hard choices are. Only as the values that inform the necessary individual and community sacrifice are articulated by the public can we expect a humane health care system.

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Information

Parietaria
A Newly Identified Cause of Pollen Allergy in California

HERBERT S. KAUFMAN, MD
San Francisco

In northern California, seasonal respiratory allergy customarily ends in late fall with conifer pollen. The last significant weeds known in the fall season to cause allergy include the chenopods, mugworts, and Compositae, and their season usually ends by the last of October.[1]

In late November 1987, a patient was seen for asthma and allergic rhinitis that had exacerbated the same month. She had been symptom-free since the previous spring. Enhanced environmental control and dietary elimination and challenge failed to alter her clinical course. During the second visit, the patient observed that beginning in mid-October, gardening in her backyard was followed immediately by symptoms. A pollinating plant with small, white blossoms and dark red stems was brought by the patient to my office. To confirm my suspicion, the plant cuttings were submitted to the botany departments of the University of California, Berkeley and Davis, where the plant was identified as *Parietaria judaica* (Barbara Ertter, Collections Manager, University and Jepson Herbaria, University of California, Berkeley, and June McCaskill, Senior Herbarium Botanist, Botany Department, University of California, Davis, written communications, December 1987). This plant is the predominant source of weed pollen allergy in Europe but not known to be a cause of allergy in the United States.

A small amount of allergy testing material was prepared in my laboratory by using Coca's extracting fluid. Prick testing with 1:40 dilution of the extract from pollen of blossoms provided by the patient produced a greater than 1 cm by 0.6 cm pseudopod reaction surrounded by 0.8 cm erythema. A larger reaction was produced by skin testing with a 5% solution of *P judaica* and *Parietaria officinalis* antigen obtained from Italy.* A similar skin test reaction occurred when a 1:40 extract of the leaves and stems was applied. The control was negative. Ten grass-sensitive and five atopic nongrass-sensitive patients were nonreactive to the *Parietaria* extracts from Italy. Rebreathing from a bag containing the freshly harvested weed preceded a 25% drop in her maximal expiratory flow rate as measured by the Wright Peak Flow Meter. She blew 460 liters per minute, 30 liters less than her predicted value and 100 liters more than her performance following rechallenge with a weed-filled bag.[2] At a later date the maneuver was carried out substituting cuttings of pollinating Monterey pine boughs. This time there was no change in her flow rates. In late December, the plant blossoms wilted, as did the patient's symptoms.

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(Kaufman HS: *Parietaria*—A newly identified cause of pollen allergy in California. West J Med 1989 Mar; 150:364-365)

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Parietaria derives its name from the Latin *parietarius*, "of walls," where the plant likes to grow, as Pliny knew when he described it,[3] and where it thrives along the wall fence at the home of this patient (Figure 1).

Parietaria is especially a problem as a cause of allergy in the south and west of Europe.[4,5] It harbors no needles but belongs to the Urticaceae family, which includes nettle plants. Three other major species, *Parietaria floridana*, *Parietaria pensylvanica*, and *P judaica*, are widespread in the United States.[6,7] *P judaica* is a wind-pollinated perennial weed that represents only 1 of at least 500 other species in its family.[8] There is thought to be no cross-sensitivity of the two allergy-causing genera of Urticaceae (*Parietaria* and *Urtica*)[9]; however, *Urtica*-positive tests were reported in 1873 by Blackley when he did the first skin test.[10] *Parietaria* has been identified in the United States for 180 years and in northern California for more than 65 years.[7] A review of early American allergy texts finds no mention of *Parietaria* as a cause of

Figure 1.—A *Parietaria* plant is shown growing in a yard near the geographic center of San Francisco. A unique characteristic of the leaves is the way in which the veins come off in an alternate rather than a symmetric pattern. The floral buds, which look like small hot cross buns, are attached directly to the maroon stems. When ripe, the buds burst open to emit a fine, creamy yellow pollen (photograph by author).

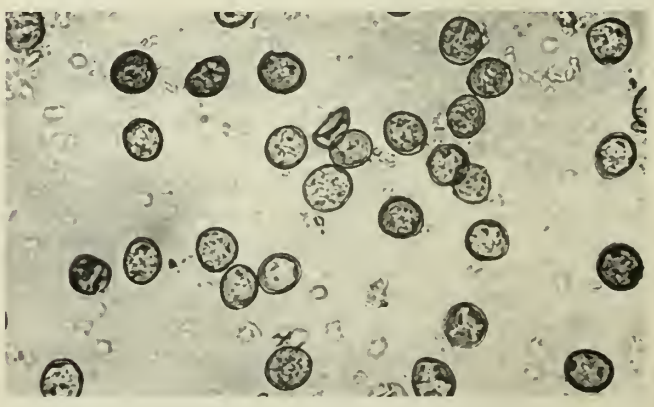

Figure 2.—The expanded spherical pollen of *Parietaria* is typically 15 μm in diameter. The specimen was prepared by Berkeley Biologicals, Berkeley, California, from cuttings submitted in November 1987. Visualization of its smooth, thin exine is enhanced using Calberla's basic fuchsin stain. By using Kodak Technical-Pan 6415 film, the coarse granular protoplasm is more easily seen within the pollen grains (original magnification × 400; photograph by author).

allergy in the United States.[11-16] There are no reports of skin test reactions or of respiratory sensitivity to *Parietaria* in this country according to the MEDLINE data base from 1967 to 1988.[17]

On a house call to the patient's home, I found the plant growing along both sides of the back wall of the yard and against the garage. The weed was found around the perimeter of the next-door-neighbor's yard in greater abundance. The neighbor volunteered that she was currently a patient in the allergy clinic at a large teaching hospital in San Francisco where the cause of her asthma is unknown. A six-block area was surveyed, and *Parietaria* was located growing in many front yards and vacant lots encircling the patient's home. Another search for the plant found it growing near the geographic center of the city. Eight years ago, a European allergist reported *P judaica* growing at the Fisherman's Wharf area of San Francisco.[18]

It is not known if the case reported here is an isolated problem. The distribution of *Parietaria* in northern California and the frequency of skin test reactivity among atopic subjects are currently under investigation. Why has *Parietaria* in California not been associated with symptoms before? The explanation may be that when the pollen is examined under a microscope, it appears very much like mold unless properly stained (Figure 2).[19] The question is whether something has occurred in the atmosphere, the character of the plant has changed, or there has been a change in the response of the host. Physicians treating patients with respiratory allergy should be vigilant for this previously unidentified cause of asthma and allergic rhinitis.

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Lessons From the Practice

From Parenthood Toward Physicianhood

MICHAEL L. CARL, *Davis, California*

No one event changes a person's life with greater swiftness than the birth of a child. Life becomes a realm of new responsibilities filled with moments of limitless joy and inevitable times of sorrow and pain. One of a parent's most difficult tasks is accompanying a child through a hospital stay.

Christina came into our lives in 1980 with tremendous abruptness. My wife, Susan, and I had scarcely enjoyed the happiness of receiving the baby girl we dreamed of when the attending pediatrician relayed that ever-foreboding news of a severe heart murmur. At that time in our lives, we were blessed with an ignorance of the implications of the news and qualified our happiness with, "She has a heart murmur, but it's probably nothing, and is she ever a beautiful little girl!" She really was, funny blue color and all, and, despite the commotion of personnel and equipment swarming about her in the neonatal intensive care unit, we never lost sight of our hopes and dreams for her.

The confusion and despair during the days following her birth were punctuated by our many decisions, made with helpless reliance on a team of physicians who were complete strangers. Christina had been catheterized the night of her birth and diagnosed as having tetralogy of Fallot with pulmonary atresia. She required immediate infusion with prostaglandins to keep the ductus arteriosus patent and then palliative surgery—a Blalock-Taussig shunt—to give her a chance for survival. In discussing the options of treatment with the pediatric cardiologist, the reality of the situation began to hit us. He carefully offered us the choice to decline the prostaglandins and the difficult operation. He pointed out that this was just the beginning of a long, uncertain future, sure to be full of hospital stays and subsequent operations. I thanked him for his honesty and explained that this was my little girl and that she had to be given every possible chance to live. There was, in reality, no choice to be made.

Christina's first operation at 2 days of age was a success, and five days later, she came home. Her second catheterization and operation occurred only ten months later, with no warning. Her shunt was rapidly occluding, and a second one had to be established as soon as possible.

After receiving this uninvited news, we were asked by the cardiologist to talk to a couple whose 3-day-old daughter was diagnosed as having transposition of the great vessels and tricuspid atresia. They were stunned by the news and not coping well. The meeting between us led to a deep relationship of support and friendship. Together, we helped each other through our daughters' operations and established a support network of families with cardiac children.

In 1985 Christina had a further corrective open-heart surgical procedure. It was a long and difficult one, taking almost eight hours. A homograft was installed as a pulmonary valve and trunk, and complete arterioplasty of the pulmonary arteries was done. For three days after the operation, Christina suffered tachyarrhythmia and tachycardia, culminating in a cardioversion to reestablish sinus rhythm. She spent three weeks in the hospital this time.

Perhaps the greatest insights I have harvested from our experiences with Christina's hospital stays have been the tender value of human life and the incredible strength of will parents can summon for the sake of their child. Sending a child into surgery or enduring the grips of chemotherapy can often become a commonplace occurrence for medical personnel. Yet, for the parents, it is an unequaled trial in which they are asked to put all of their dreams for the future on hold in the hope that there will be a future. When Christina was taken down to the operating suites for her corrective surgical procedure, my wife and I rode in the elevator with her. When we reached the basement, the doors opened synchronously with the elevator across the hallway, and we came face to face with a young couple accompanying their 3-year-old son to open-heart surgery also. The images of their faces will remain with us forever. It was as though we were looking in a mirror, seeing the red, blurred eyes, the ashen look of despair. Somehow, parents find the strength or determination it takes to get through these times, all the while exhibiting a facade of confidence and composure for our children. In reality, we are just as frightened—perhaps more so—as they are.

I am just one parent who did what it took for his child. There are so many more who, every day, face their children's suffering. I hope that when I am a physician, I can learn from them.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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(Carl ML: From parenthood toward physicianhood. West J Med 1989 Mar; 150:366)

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SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294, or 1 (800) 234-1231.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

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CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural lifestyles. Contact Dr Donn Cobb, Health Officer, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee-for-service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

ORTHOPEDIST. One day per week. Medical-legal evaluations for traumatic injury patients. No surgery. California license required. Lucrative fee-for-service with high growth potential and guaranteed base. Contact Director, PO Box 14046, San Francisco, CA 94114.

NEW MEXICO. Physicians to share management of general and orthopaedic surgical patients with BC specialists in U.S. Government hospital serving native Americans. Competitive salary and generous fringe benefits. Opportunity to learn, broaden professional capabilities, and enjoy Southwest. Contact E. K. Mehne, MD, Gallup Indian Medical Center, Gallup, NM 87301; (505) 722-1210.

EUGENE, OREGON. Family Physicians, BE/BC, sought to join growing 36 physician Family Practice/Internal Medicine group in Eugene and nearby rural Cottage Grove. OB optional. Excellent OB support available. Initial income guarantee with incentive. Partnership anticipated after two years. Outstanding schools. Abundant cultural and recreational opportunities. Please send CV or call Rob Daugherty, MD, Oregon Medical Group, 78-A Centennial Loop, Eugene, OR 97401; (503) 688-9140.

OREGON. General Internist (BC/BE) sought for busy practice. 10 member multispecialty group. Beautiful rural community. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 471-6161.

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CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN, Oncologist, or Infectious Disease Specialist at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

PULMONOLOGIST. Pulmonologist wanted as associate in very busy Pulmonary/Critical Care practice in Kern County, California. Practice is 100 percent Pulmonary/Critical Care and includes Pulmonary Consultation, Pulmonary Physiology Laboratory, Pulmonary Rehabilitation, Respiratory Care, state-of-the-art Sleep Lab available. Excellent opportunity for BC/BE Pulmonologist looking for potential partnership. Those interested please send CV and inquiries to Dale T. Herriott, MD, Inc, 2525 Eye St, Ste 2B, Bakersfield, CA 93301.

(Continued on Page 372)

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CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

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  The low incidence of side effects with Cardizem allows patients to feel better.
- **Protection against angina attacks**[1,5,7-9]
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- **A decrease in myocardial oxygen demand**
  Resulting from a lowered heart rate-blood pressure product.[5]
- **Compatible with other antianginals**[6†]
- **Safe in angina with coexisting hypertension, COPD, asthma, or PVD**[1,3,5,6]

60 mg GREATER DOSAGE FLEXIBILITY 90/120 mg

**CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.*

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

1419H8

CARDIZEM® diltiazem HCl/Marion

ANTIANGINAL PROTECTION PLUS SAFETY

Rx
Cardizem® (diltiazem HCl)
☐ 60 mg ☐ 90 mg
☐ 120 mg
Sig: tid

Usual maintenance dosage range: 180-360 mg/day

BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission

WARNINGS

1 **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem

2 **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients

3 **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4 **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic	Petechiae, pruritus, photosensitivity, urticaria.
Other	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

References: **1.** Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whitlie J, et al: Am J Cardiol 1982;49:554-559.

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SPECIAL ISSUES

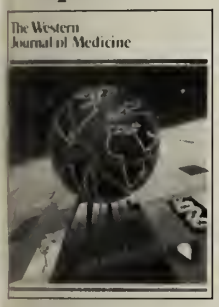
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

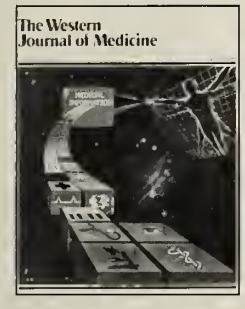
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



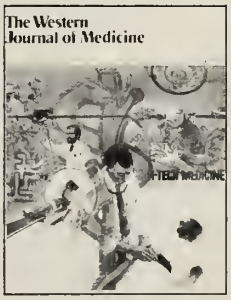
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



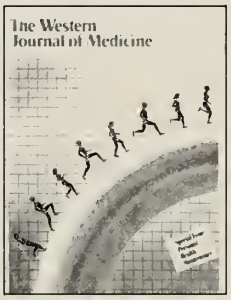
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



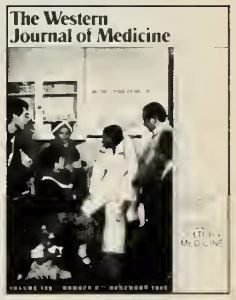
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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(Continued from Page 368)

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FAMILY PRACTICE, PHOENIX, ARIZONA. BC/BE, private practice, no OB. In-office lab and x-ray. Growing area, southwestern life-style at its best. Located across from modern, full-service hospital. Call (602) 846-7500 or résumé to Westside Family Practice, 5251 W. Campbell Ave, #105, Phoenix, AZ 85031.

NEUROLOGIST BC/BE. Needed to join rapidly expanding multispecialty group practice in Reno, Nevada (population 350,000). Fee-for-service and pre-paid health care. EEG, EMG, and general Neurology practice with active clinic and hospital bases. Excellent compensation and benefits package including stock options, paid malpractice, and relocation expenses. Interested individuals should submit a CV in confidence to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645, Attn: Janet R. McGee, Manager, Physician Recruitment.

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SAN JOSE, CALIFORNIA. Pre-paid medical group (HMO) looking for dynamic BE/BC residency trained Family Physician. Extensive fringe benefits, including malpractice coverage. Immediately available opening. Send CV to James Conroy, MD, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119; or call (408) 972-6339.

INTERNIST BE/BC to join growing practice in Tacoma, Washington. Practice is oriented to women's health issues. Women encouraged to apply. Send CV to PO Box 2122, Gig Harbor, WA 98335; (206) 858-8686 evenings.

NORTHERN CALIFORNIA. Family Practice opportunity with Community Health Center. Modesto location. Salary plus incentive program. Spanish fluency desirable. Contact Michael Sullivan, Executive Director, Merced Family Health Centers, Inc, PO Box 858, Merced, CA 95341; (209) 383-1848.

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

WESTERN WASHINGTON. Otolaryngologist with ENT-Allergy. Sea-ski-golf-fish-hunt-garden etc. Mild climate, good schools, low crime, good location, smaller community, large drawing area. Excellent hospital. Will work with you to help establish. Well equipped office, good crew. Reply to Number 135, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PRIMARY CARE INTERNIST OR FAMILY PRACTITIONER—BC/BE to join busy expanding fee-for-service/HMO practice in Thousand Oaks, attractive city of 100,000 in Ventura County. Competitive salary and benefits with eventual optional partnership. CV to Sterling Piepgrass, MD, 1400 W. Hillcrest Dr, Newbury Park, CA 91320; (805) 499-1937. Immediate opening.

FAMILY PRACTICE—CENTRAL IDAHO. BC/BE to join hospital managed practice. Salary guarantee plus incentive. All expenses of the practice are paid by the hospital. Low-key practice with boundless recreational opportunities available. Contact John Hull, Administrator, St Mary's Hospital, Box 137, Cottonwood, ID 83522; (208) 962-3251.

OREGON COAST. Busy fee-for-service multispecialty group looking for additional Internist and Family Practitioner including OB to work with two Internists and three Family Practice Physicians. Well-equipped clinic next to 34-bed hospital with eight ICU/CCU beds and two new birthing rooms. Top-notch school system and just 75 miles to Portland. Send CV or call Rick Bigger at North Coast Medical Center, PC, 727 Wahanna Rd, Seaside, OR 97138; (503) 738-9551.

WANTED. BC/BE Internist or Family Practitioner to join three man, well-established primary care group in San Francisco. Excellent opportunity, early partnership. Call or write John Pierce, MD, 3620 Army St, San Francisco, CA 94110; (415) 826-7575.

SUN VALLEY, IDAHO. Diagnostic Radiologist for Mountain Resort Hospitals needed to join one other. Experienced in General Diagnostic, Orthopedic, US and Doppler, NM, and CT. Contact R. Dennis Davis, MD, Box 242, Sun Valley, ID 83353, or phone (208) 622-3323, ext 165.

FAMILY PRACTICE, PUGET SOUND. 27 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

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VENTURA (VENTURA COUNTY). Multispecialty group of 42 physicians has an opening for a BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

BC/BE GENERAL INTERNISTS needed for multispecialty group in Sacramento, California. We are an established Department of Medicine with close university affiliation. Pleasant practice setting where physicians are free to practice the highest quality medicine with full access to diagnostic, therapeutic, and consultative services. Our patients are from a growing Sacramento community with a good cost of living. Our hospital provides a substantial part of University of California Davis residency training program. Excellent in-house continuing medical education program. We are a successful, stable medical group experiencing robust growth. Outstanding starting salary and advancement. Full benefits and retirement. This is a quality career opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, 2025 Morse Ave, Sacramento, CA 95825.

(Continued on Page 374)

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(Continued from Page 372)

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Or call (209) 252-3047.

BC/BE INTERNIST. In northern California wine country. Join two man group in private practice of Internal Medicine. Subspecialty interest OK. Reply to Number 138, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA SIERRA FOOTHILLS. Vascular/General Surgeon BC/BE to join established Surgical group. Send CV to Number 137, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGIST, NONINVASIVE OR INVASIVE. BC/BE to join busy solo Invasive Cardiologist in San Jose, California. Excellent benefits and early partnership opportunity for motivated Cardiologist. Expertise required in echo Doppler, stress testing, Swan-Ganz and pacemaker insertion. San Jose is located 50 miles south of San Francisco, close to numerous cultural and recreational opportunities. Please send CV to Number 136, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

LAGUNA BEACH, CALIFORNIA. BE/BC Internist to join three established primary care Internists. Immediate opening in private practice association. Send CV to Paul H. Prewitt, MD, Ste 204, 31862 Coast Hwy, Laguna Beach, CA 92677.

ORANGE COUNTY, CALIFORNIA—FAMILY PHYSICIAN. There are several busy, well established Family Physicians here now seeking associates, or someone to share space and call. Financial assistance for latter option. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-3C, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

PACIFIC NORTHWEST OPPORTUNITIES

These attractive private practice opportunities are now available in Tacoma, Washington, a community of 160,000 on Puget Sound, just south of Seattle:

INTERNISTS—Affiliate with five busy, solo Internists involved in primary care. These physicians also desire to affiliate with an Internist interested in Geriatrics. Or, take the opportunity to affiliate with three women Internists with strong emphasis on women's health care. Broad-based subspecialty backup.

ORTHOPEDIC SURGEON—Two well-established Orthopedic Surgeons are seeking to add an associate with interest/experience in back surgery.

UROLOGIST—A busy Urologist is seeking an associate to join his expanding practice.

For further information, send your CV to: Gordon Crawford, Professional Relations, Humana Inc., Dept. HH-3, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

Humana®

PHYSICIANS WANTED

SEATTLE AREA

GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

Allergy	Ophthalmology
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Family Practice	Psychiatry
General and Vascular Surgery	Urgent Care
OB/GYN	Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

FAMILY PRACTITIONERS AND INTERNISTS needed part-time for staffing ambulatory care clinic. Our clinic operates seven days a week during days and evenings and provides episodic care on a same-day basis. Our patients are from a growing Sacramento community with good cost of living. Physicians may choose to work one to 10 half-days or evenings per week with wide flexibility. Full benefits and retirement if working six or more half-days a week on a steady basis. We are a successful, stable medical group experiencing robust growth. Please call John Petitt, MD, (916) 973-5560 or send CV to John Petitt, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825.

WESTERN WASHINGTON—without the rain. Low volume Emergency position in Anacortes. Close to San Juan Islands, North Cascades, Seattle, Vancouver. $80,000 plus malpractice. Call Bob Apter, MD, FACEP, (206) 466-3327.

HEMATOLOGIST/ONCOLOGIST. Well established HMO located in beautiful northern California wine country seeking Oncologist and Hematologist/Oncologist. Excellent salary, benefits, security, and ample time off. Please send CVs to Richard Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

VENTURA (SOUTHERN CALIFORNIA). Multispecialty group of 42 physicians has a position available for a BC/BE Psychiatrist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Psychiatrist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (VENTURA COUNTY). Multispecialty group of 42 physicians has immediate positions available for two BC/BE Family Practitioners. Openings are available in each of our offices, located in Ventura, Camarillo, and Oxnard. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Family Practitioner, 2705 Loma Vista Rd, Ventura, CA 93003.

TUCSON, ARIZONA PRACTICE OPPORTUNITY for BC Family Physician to join busy solo Family Practitioner. Lucrative incentive startup package available. Contact Herbert R. Jalowsky, MD, 1701 W. St Mary's Rd, Tucson, AZ 85745; (602) 622-1414.

BC/BE FAMILY PRACTITIONER for nonprofit community clinic in redwood country. Prefer OB/Pediatrics training, but OB negotiable. C-sections optional. Quality care for underserved and more affluent in rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

INTERNIST, University trained, wanted to join three physician group in the heart of the beautiful coastal redwoods. Active, varied, quality practice in a friendly community far from the city's woes, yet one hour by plane from San Francisco. Send CV to Timm Edell, MD, 2773 Harris St, Eureka, CA 95501.

MID-LEVEL PRACTITIONER, FNP/PAC, bilingual Spanish/English, for general medical lesbian health clinic. CV to Lyon-Martin Women's Health Services, 2480 Mission St, #214, San Francisco, CA 94110.

FREE-STANDING EMERGENCY AND GENERAL MEDICAL CENTER in northern California college town seeks physician with Emergency Room/Family Practice experience. Very attractive compensation. Contact Roy Grossman, MD, (916) 891-1676.

INTERNAL MEDICINE. Kaiser Permanente office in central California, rapidly growing new market area, seeking BC/BE Physicians in the Department of Medicine. Address inquiries to Antonis Antoniou, MD, Assistant Physician-in-Charge, Kaiser Permanente, 4785 N. First St, Fourth Floor, Fresno, CA 93726; (209) 221-4944.

INTERNAL MEDICINE. BC female Internist with successful established practice in the San Gabriel Valley of southern California seeks BC/BE energetic, imaginative Internist as associate. No investment. Guaranteed salary plus. Send CV/letter to SGHS, PO Box 2114, San Gabriel, CA 91778.

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PHYSICIANS WANTED

FAMILY PHYSICIAN—SAN DIEGO

Well-established (40 years) three Family Practitioner group seeks Family Practitioner to replace retiring associate. Attractive salary plus incentives. Possibility of partnership after two years. Well-rounded Family Practice—Pediatrics to Geriatrics. Send CV to **Gordon Lillie, MD, 7043 University Ave, La Mesa, CA 92041.**

LOS ANGELES COUNTY—FAMILY PHYSICIAN. There are now two attractive opportunities for Family Physicians in the Los Angeles area. Join a busy, five member group or select a salaried position in a small urgent care center. For more information, send your CV to Manager, Professional Relations, Humana Inc, Dept HH-3A, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

UROLOGIST—LOS ANGELES AREA. A busy, well established three physician group of Urologists in the Los Angeles area is now seeking to add another member. For more specific information about this private practice opportunity, call toll-free 1 (800) 626-1590, or send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-3B, 500 W. Main St, Louisville, KY 40201-1438.

INSTRUCTOR, MEDICINE. Instruct students in medicine in the Department of Acupuncture and Oriental Medicine. Develop and prepare course outlines, study materials, plan and implement curriculum and class schedules in cooperation with faculty staff. Conduct classes including lecture, seminar and laboratory services. MD or BS in medical studies. No experience required. Salary $3,275 per month. Job site/interview, Los Angeles, California. Send this ad and your résumé to job #WS16328, PO Box 9560, Sacramento, CA 95823-0560 not later than April 9, 1989.

EASTERN WASHINGTON. Need career practice change? Eastern Washington community, population 115,000. Semi-arid with vast water resources for recreation, irrigation, and power. Economically diverse agriculture and energy base. Family Practice, Oncology, Pulmonology, Urology, Pediatrics, and Psychiatry needed. Rapid practice start-up. Support package available. Financially sound 102-bed hospital. Send CV or call Kathleen E. Street, The Friedrich Group, 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 842-5248.

FACULTY POSITIONS. The San Jose Medical Center Family Practice Residency Program has an opening for full-time and part-time faculty. Positions include direct patient care (including OB), resident teaching and administrative duties. Program affiliated with Stanford University School of Medicine. Competitive salary and benefit package. Please direct inquiries to Robert Norman, MD, Director, 25 N. 14th St, Ste 1020, San Jose, CA 95112; (408) 977-4507.

PHYSICIANS WANTED

CAN YOU AFFORD TO MISS THIS OPPORTUNITY?

INTERNAL MEDICINE/FAMILY PRACTICE POSITION IN SOUTHERN CALIFORNIA

Enjoy a professional, challenging, growth opportunity with successful Internal Medicine private practice.

This position offers an excellent guarantee, bonus, malpractice, benefits, CME, and partnership potential.

Located in a lovely suburban community in southern California.

Send inquiries and CV to:

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Physician Recruiters
250 N. Robertson Blvd, Suite 405 • Beverly Hills, CA 90211
(213) 277-7331 / (800) 922-7PHY

MEDICAL RESEARCHER. Duties: Determine the effects of x-rays on cochlea and the complications of x-rays on the ear regarding deafness. Analyzing of reports of medical staff and analyzing results of the x-rays. No treating or examining of patients. Education: MD, PhD, or equivalent. Rate of pay: $5,150 per month; overtime: time and a half. 40 hours per week. Two years experience. Job site: Encino, California. Send this ad and a résumé to Job #FHC 2113, PO Box 9560, Sacramento, CA 95823-0560 not later than April 9, 1989.

LARGE MULTISPECIALTY PRIVATE GROUP PRACTICE RECRUITING FAMILY PRACTITIONER. Must be BC/BE. Excellent opportunity for qualified physician in very desirable high growth area of southern California. Congenial staff, excellent working conditions, and fringe benefits. Salary negotiable. Submit CV to George W. Kanaly, PhD, President, Riverside Medical Clinic, 3660 Arlington Ave, Riverside, CA 92506.

CALIFORNIA. Full-time Emergency Medicine attending position available at 233-bed teaching hospital in the heart of the San Joaquin-Sacramento River Delta. $75,000-100,000 plus per year with flexible scheduling, camaraderie, and paid malpractice. Send CV to Richard Buys, MD, PO Box 1020, Stockton, CA 95201 or call (209) 468-6818. Affirmative Action/Equal Opportunity Employer.

GENERAL INTERNIST. Well established HMO located in beautiful northern California wine country seeking General Internist. Excellent salary, benefits, security and ample time off. Please send CVs to Richard Zweig, MD, at 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

ASSISTANT ASSOCIATE PROGRAM DIRECTOR for Family Practice program. Must have AAFP Boards. Would like private practice experience, but will evaluate applicant's overall strengths and will waive practice requirement in selected candidates. Strong program. University (University of California, Davis) affiliated. Excellent opportunities in research, curriculum development, and teaching of clinical skills. Call or send CV to Bruce Nichols, MD, Director of Family Practice, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6834. AA/EOE.

FAMILY PRACTICE. Family Practice Physician sought by large medical group for a rural satellite location 15 miles from Sacramento. Competitive salary and benefits first year. For more information, please send current CV to Warren J. Boyer, Jr, MD, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

NORTH CALIFORNIA BE/BC INTERNIST wanted to join busy solo practice part- or full-time in Sierra foothills. Send CV to Number 143, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

HEMATOLOGIST/ONCOLOGIST, WASHINGTON STATE BC/BE. Immediate opportunity to take over established practice within the Hematology/Oncology (three and one-half physician) Division of the Rockwood Clinic, a 60 member multispecialty group. Competitive salary and benefits leading to early shareholder status. Spokane (metropolitan population 350,000) offers affordable housing, excellent schools, cultural activities, and unlimited outdoor recreation. Send CV to Colleen Mooney, Recruitment Coordinator, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119 or phone (408) 972-6560.

GENERAL SURGEON BC for full-time staff of specialty oriented referral hospital of Indian health service. Competitive salary and generous fringe benefits, reply to E. K. Mehne, MD, Gallup Indian Medical Center, Gallup, NM 87301, or (505) 722-1000. EEO employer.

(Continued on Page 377)

PART-TIME MEDICAL CONSULTANT CONTRACTS

Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 75 Hawthorne St, San Francisco, California. No patient contact. Applicants must: (1) have a valid license to practice medicine in the USA; (2) have recent or current clinical experience; (3) be available approximately 8-20 hours per week between 7:00 a.m. and 4:30 p.m., Monday through Friday for case review; and (4) reside within 30 miles of San Francisco. Interested applicants may be interviewed. Finalists will be interviewed. Subject to change, the specialties needed are Psychiatry, Neurology, Internal Medicine, Psychology, Orthopedics, Pediatrics, Rheumatology, and Otolaryngology. Women and minorities are encouraged to apply.
***If interested in receiving further information, call* (415) 556-4351, Disability Programs Branch, SSA, or submit a written request by March 30, 1989, to Chief, Regional Acquisition Management Branch, 50 United Nations Plaza, Room 403, San Francisco, CA 94102.**

(Continued from Page 376)

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

FAMILY PRACTICE PHYSICIAN needed at community clinic serving a primarily low income, ethnically and culturally diverse population. Practice includes OB and in-patient attending responsibilities, consultation with mid-level providers, and a faculty position at the University of Washington. BE or BC required; bilingual English-Spanish desired. If interested send résumé or contact Sharon Dobie, MD, or Rich Kovar, MD, (206) 461-4518, Country Doctor Community Clinic, 500 19th Ave E, Seattle, WA 98112.

WESTERN COLORADO. Assistant Director wanted for innovative Family Practice program. Must have primary interest in OB and Maternal/Child Care. Should be BC in Family Practice, teaching experience preferred. Contact Dr Daniel R. Dill, 2333 N. Sixth, Grand Junction, CO 81501; (303) 244-2195.

THIRD GASTROENTEROLOGIST for HMO in northern California wine country. Excellent salary, fringe benefits and life-style. Contact Richard Permutt, MD, 401 Bicentennial Way, Santa Rosa, CA 95403.

INTERNAL MEDICINE. San Francisco bay area—immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical housestaff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

MINNESOTA, IOWA, AND WISCONSIN group practice positions are available for BE/BC physicians in the following specialties: Family Practice, Internal Medicine, Occupational Medicine, Pediatrics, and Obstetrics/Gynecology. Competitive salary with benefits. Send letter of inquiry and CV to Scott M. Lindblom, Fairview Clinic Services, 2312 S. 6th St, Minneapolis, MN 55454; or call (612) 371-6235, or toll free 1 (800) 328-4661, ext 6235. An Equal Opportunity Employer.

SAN FRANCISCO BAY AREA

BE/BC Internist. We currently are seeking highly qualified Internists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV:

Winslow Wong, MD
Chief, Department of Internal Medicine
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

PHYSICIANS WANTED

ARIZONA. BE/BC Family Practitioner sought for Primary Care center 15 miles northwest of Tucson. Salary/benefits negotiable. Malpractice paid. Contact Medical/Executive Director, Marana Health Center, 13644 Sandario Rd, Marana, AZ 85653; (602) 792-0898.

INTERNIST to join three man group in Alaska's southernmost city, Ketchikan. Long established medical practice. Boating, sailing, hiking, and fishing and hunting in season. Guaranteed salary and excellent benefits. Send CV to Arthur Wilson, Jr, MD, Box 8678, Ketchikan, AK 99901; (907) 225-4104.

NAPA, CALIFORNIA. BC Internist. Location in Napa, heart of the wine country. Close to San Francisco. Offering start-up in personal private practice. Send CV and two letters of recommendation (Department Chief if applicable) to Alvin L. Block, MD, 3230 Beard Rd, Napa, CA 94558; (707) 257-1550.

NONINVASIVE CARDIOLOGIST. BC/BE Cardiologist for busy Invasive and NonInvasive Cardiology practice. Currently the only such practice in a service area with a population of 127,200. Prefer training in Echocardiography and Nuclear Medicine. Referral area located in a scenic mountain valley, a college community with a wide variety of cultural, educational, sporting, and commercial opportunities. Contact Tom Welter, Senior Assistant Administrator, Logan Regional Hospital, 1400 North 500 East, Logan, UT 84321.

OBSTETRICIAN/GYNECOLOGIST, NEUROLOGIST, NEUROSURGEON for progressive multispecialty group of over 21 physicians within one and a half to three hours of the San Francisco bay area, Yosemite, and Lake Tahoe. Tracy, located in the San Joaquin Valley, has a diversified economy with excellent schools. Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package including malpractice insurance. Reply with CV and references to Physician Recruitment, Eaton Medical Group, 445 W. Eaton Ave, Tracy, CA 95376.

OCCUPATIONAL/FAMILY PRACTICE. The Pacific northwest's leading outpatient medical provider has opportunities for Primary Care Physicians to join an expanding 150 person medical group. Full/part-time openings throughout California and Seattle-Tacoma, Washington. Prior outpatient/occupational experience preferred. Attractive package includes competitive base salary plus incentive program, malpractice insurance, comprehensive benefits, 401(k) plan, vacation/sick/holiday/CME. Opportunity for advancement for energetic, hard-working physician committed to quality health care. Join our dynamic team of health care professionals. Contact Robin Smith, Director, Personnel, ReadiCare/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

INTERNIST. Long established multispecialty group in Arcadia, California looking for General Internist, BC/BE. Excellent career opportunity. Send CV or call J. Steinmetz, Administrator, Arcadia Medical Clinic, 1108 S. Baldwin Ave, Arcadia, CA 91006; (818) 446-8831.

ACADEMIC GENERAL INTERNISTS. Assistant/associate professors involved in teaching/research in ambulatory care. Protected time and research design curriculum offered. Must be eligible for licensure in Nevada and BE/BC. Send CV/names of three references by April 1, 1989 to Philip Goodman, MD, Department of Internal Medicine, University of Nevada School of Medicine, Reno, NV 89557; (702) 784-4614. Position open until filled. AA/EOE.

CHIEF RESIDENT—1989-1990. Strong primary care emphasis. Must be eligible for licensure in Nevada. Benefits include special training in research design and statistics. Please call or send CV to Steven Zell, MD, Dept of Internal Medicine, University of Nevada School of Medicine, Reno, NV 89557; (702) 784-4614. AA/EOE.

PHYSICIANS WANTED

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, General Internal Medicine, Neurology, General Surgery (breast disease focus), OB/GYN. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Dr Larry W. Hirons, Medical Director
1162 Willamette St
Eugene, OR 97401

FAMILY PRACTICE, EMERGENCY AND OCCUPATIONAL MEDICINE. Primary Care Physician BC/BE in specialty to join Family Physicians in providing Primary Care and Occupational Medical services in an urgent care setting in the San Joaquin Valley. Competitive salary with incentive plan. Paid malpractice. Equity position possible after one year. Send CV to Janice Storey, Southwest Urgent Care Center, 5397 Truxtun Ave, Bakersfield, CA 93309; (805) 322-2273.

OB/GYN NORTHERN CALIFORNIA. Position available for BE/BC OB/GYN in 10 person department with new LDR suite, family centered Obstetric practice as well as full Gynecology practice. 20 miles south of San Francisco, adjacent to large wooded areas, and easy access to ocean. Prepaid medical group with competitive salary and very generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented (first year guaranteed $70,000) with advancement to full partnership after one year. Excellent fringe benefits. If interested. CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

BE/BC UNIVERSITY TRAINED ONCOLOGIST/INTERNIST to join well established San Francisco bay area HMO. Excellent salary and benefits. Outstanding educational and recreational opportunities in a choice location. Contact David Lakes, MD, Chief, Department of Oncology, Kaiser Permanente, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

FAMILY PRACTICE/SACRAMENTO. Due to continued growth, positions for Family Practice are now available at Kaiser Permanente Medical Center, south Sacramento. Our salary is very competitive and we have an outstanding retirement and benefits package. Your practice at Kaiser will allow insulation from the headaches and financial uncertainty of private office practice, while fostering your professional growth at a first rate medical center. For further information, please contact Jack Berger, MD, Assistant Chief, Department of Medicine, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823; or call (916) 686-2267.

WASHINGTON, CASCADE MOUNTAINS. Three physician Family Practice seeking fourth Family Practitioner. Challenging rural practice in recreational area 80 miles east of Seattle. Interest in Emergency Medicine necessary, OB optional. Ski areas, lakes, wilderness, and pleasant family oriented community. Contact Paul Schmitt, MD, 201 Alpha Way, Cle Elum, WA 98922; (509) 674-5331.

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PHYSICIANS WANTED

FAMILY PRACTITIONER. Multispecialty group located in San Luis Obispo, California on the central coast, seeking a BE/BC physician. Fringe benefits plus practice costs paid and immediate shareholder status. Submit your CV to Administration-Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

ORTHOPAEDIC SURGEON, Orthopaedic office, Oakland, California. Office practice only. Flexible schedule. Industrial and medical-legal practice, including patient care and writing reports. Remuneration and benefits negotiable. Send résumé to Number 145, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSIATRIST, Orthopaedic office, Oakland, California. Office practice only. Flexible schedule. Industrial and medical-legal practice, including patient care and writing reports. Remuneration and benefits negotiable. Send résumé to Number 146, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA. The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. University associated residency program. Competitive salary and comprehensive benefits package. 90 miles from San Francisco and Sierra skiing. California license required. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678.

SAN FRANCISCO. Primary care Internal Medicine including HIV patients and opportunity for research. Contact Carol Sweig, WPR, 710 Van Ness, San Francisco, CA 94102; (415) 673-7676.

WASHINGTON. Openings for career oriented Emergency Physicians, BE/BC in Emergency or Primary Medical specialty. In a Seattle metropolitan hospital with 48,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 S. 43rd St, Renton, WA 98055.

RESEARCH ASSISTANT PROFESSOR. Division of Endocrinology, Department of Medicine at University of Washington seeks a PhD scientist specializing in neural control of insulin and glucagon secretion. Preference given to those with demonstrated experience in performing independent research and in developing both RIAs for neuropeptides and whole animal models. Should be at least four years post-doctoral and have personal grant support. Send CV and references by March 22 to Dr G. J. Taborsky, Jr, Division of Endocrinology (151), Seattle VA Med Center, 1660 S. Columbian Way, Seattle, WA 98108. AA/EOE.

GENERAL INTERNIST, with or without subspecialty training, being sought to join busy seven member Internal Medicine practice in downtown Sacramento. One to two years of guaranteed salary to start. Contact Joshua Hoffman, MD, at (916) 733-5097, or send CV to 2801 K St, #520, Sacramento, CA 95816.

INTERNAL MEDICINE. PGY II/III positions available in July 1989, in bay area county hospital, Stanford affiliated. Send CV to Department of Medicine, 750 S. Bascom Ave, San Jose, CA 95128.

CLASSIFIED ADVERTISING INFORMATION

(415) 541-0900, Ext 376

PRACTICES AVAILABLE

COLORADO COLLEGE TOWN. General Internal Medicine and Geriatric practice and building for sale. $250,000, variable terms. Solo corporation. Great place to live. Call 1 (303) 482-4510 evenings.

FOR SALE, COMPLETE FACILITY. 3,200 square feet plus 1,200 square foot basement, 10 examining rooms, three consulting offices, 40 patient waiting rooms, x-ray, emergency room/minor surgery, ECG, laboratory, nurse station, coffee, computer room with Medical program and ECT block/cement construction, 50 patient and 15 employee parking, refrig/heat system. Presently two doctor General Practice, gross over ½ million. Excellent for group Family Practice, Internist, Pediatric or HMO group starter. Total price $475,000, includes real estate, equipment, supplies, and practice. Financial terms negotiable. No lease trials. Located northwest New Mexico. Write Michael Danoff and Associates, Attn: Medical, 604 Chama NE, Albuquerque, NM 87108.

CALIFORNIA, SACRAMENTO VALLEY— Family Practice. Long established three man group. Excellent area, fishing, hunting, skiing, etc. Practice collects approximately $360,000, nets $180,000. Urology practice also available. Call Western Practice Sales, (916) 673-1302.

SAN DIEGO—INTERNAL—FAMILY—OB/GYN—PEDIATRIC AND OTHER SPECIALTY PRACTICES AVAILABLE. Long established—doctors retiring. Various prices—low down payments. Call CBI, the San Diego professional practice sales specialists, (619) 283-7009.

NORTHERN ARIZONA FAMILY PRACTICE FOR SALE. Well-established, solo practice. Share in call group. Purchase office building optional. Ideal location for family—good schools, university, plenty of outdoor activities. Kirk R. Stetson, MD, Flagstaff, Arizona; (602) 774-6671.

GENERAL PRACTICE / FAMILY PRACTICE, LAKE HAVASU, ARIZONA. Illness forces sale of growing solo practice. Growing outdoor recreational community, low desert, 40 miles to lake. Hospital expansion in progress. Great income potential, plus friendly, smog-free community to raise family. Appraisal available, negotiable terms. Mrs L. Cacho, (602) 453-8211 evenings; (602) 453-1951 message.

NORTHERN CALIFORNIA INTERNAL MEDICINE practice for sale. Excellent area for work and recreation. Reply with CV to Number 144, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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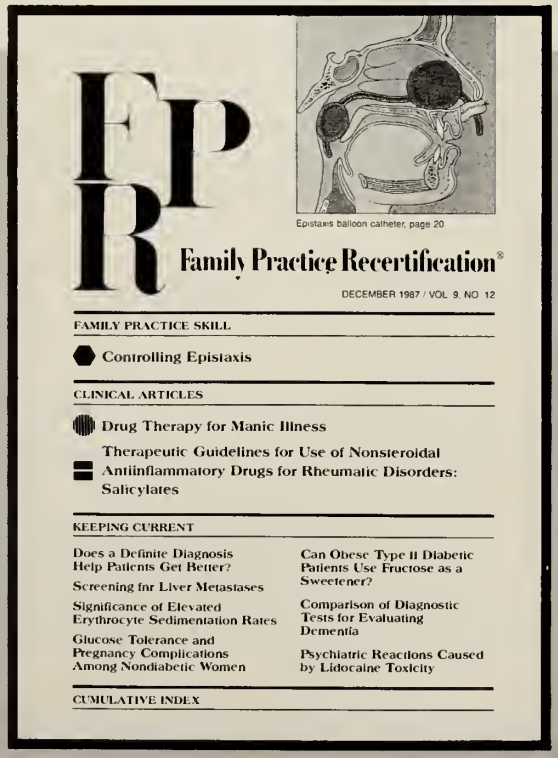

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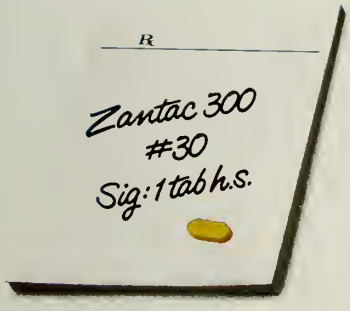

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1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
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In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

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August 1987

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The portrait of anxiety

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is often complicated

With associated depressive symptoms.

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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema.* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema. Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy – Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (79%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest; pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostate hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium <130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. JSV ST8R(815)

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1 Data on file, Lilly Research Laboratories.

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AXID®

nizatidine capsules

Brief Summary

Consult the package literature for complete information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General* — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests — False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions — No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

PV 2096 AMP [013089]

Additional information available to the profession on request.

Placebo-like side effect profile at the 1 mg dose

Real-life benefits with TENEX® (Guanfacine HCl)

1 mg Tablets

When more than a thiazide diuretic is needed

A·H·ROBINS

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: *General*. Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n=	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n=279)	Clonidine (n=278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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From the Neurology Service and Hematology/Oncology Service, Department of Medicine, Letterman Army Medical Center, Presidio of San Francisco.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

A BETTER CHANCE FOR

AN ULCER-

Well-controlled clinical trials confirm:

ZANTAC 150 mg hs significantly superior to cimetidine 400 mg hs for maintenance therapy in healed duodenal ulcers.

FREE FUTURE

Percent of patients ulcer-free after 1 year of therapy

ZANTAC 150 mg hs (n=60)	**84%***
cimetidine 400 mg hs (n=66)	**57%**
ZANTAC 150 mg hs (n=243)	**77%†**
cimetidine 400 mg hs (n=241)	**63%**

*P=0.01 †P=0.0004 % life-table estimates

All patients were permitted prn antacids for relief of pain. Adapted from Silvis[1] and Gough.[2]

These two trials[1,2] used the currently recommended dosing regimen of cimetidine (400 mg hs) and ranitidine (150 mg hs). A comparison of other dosing regimens has not been studied.
The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.
The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Glaxo/ ROCHE

See next page for references and Brief Summary of Product Information.

References: 1. Silvis SE, Griffin J, Hardin R, et al Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer *J Clin Gastroenterol* 1985;7(6) 482-487 2. Gough KR, Korman MG, Bardhan KD, et al Ranitidine and cimetidine in prevention of duodenal ulcer relapse A double-blind, randomised, multicentre, comparative trial *Lancet* 1984;2 659-662

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

The following is a brief summary only Before prescribing, see complete prescribing information in ZANTAC® product labeling

INDICATIONS AND USAGE: ZANTAC® is indicated in.
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks
2 **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3 The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis)
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy Therapy for longer than six weeks has not been studied

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution)

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: ZANTAC is secreted in human milk Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases Headache, sometimes severe, seems to be related to ZANTAC administration

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice

Musculoskeletal: Rare reports of arthralgias

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated Doses up to 6 g/day have been employed in patients with severe disease

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day

GERD: The current recommended adult oral dosage is 150 mg twice a day

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

AIDS—A GUIDE TO CLINICAL COUNSELLING—Riva Miller, AIDS Counselling Coordinator, Hampstead Health Authority, and Senior Social Worker and Family Therapist, Haemophilia Centre and Haemostasis Unit, Royal Free Hospital, and Robert Bor, District AIDS Counsellor, Senior Clinical Psychologist, and Family Therapist, Royal Free Hospital and School of Medicine, Hampstead Health Authority, London. Science Press, distributed by Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1988. 123 pages, $23.50 (paperback).

BAG BALM AND DUCT TAPE—TALES OF A VERMONT DOCTOR—Beach Conger, MD. Little, Brown and Company, 34 Beacon St, Boston, MA 02106, 1988. 263 pages, $16.95.

A COLOUR ATLAS OF HEART FAILURE—Leonard M. Shapiro, MD, MRCP, Senior Registrar, and Kim M. Fox, MD, MRCP, Consultant Cardiologist, National Heart Hospital, London. Wolfe Medical Publications Ltd, distributed by Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1988. 572 pages, $69.50.

A COLOUR ATLAS OF STROKE—CEREBROVASCULAR DISEASE AND ITS MANAGEMENT—Asif Kamal, MB, BS, MRCP, Consultant Physician in Geriatric Medicine, St George's Hospital, Lincoln, England. Wolfe Medical Publishers Ltd, distributed by Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1987. 218 pages, $79.50.

CONTEMPORARY INTERNAL MEDICINE—CLINICAL CASE STUDIES—Edited by Juan Bowen, MD, and Ernest L. Mazzaferri, MD, Ohio State University, Columbus. Plenum Medical Book Co, 233 Spring St, New York, NY 10013, 1988. 312 pages, $45.

DATA ANALYSIS FOR CLINICAL MEDICINE: THE QUANTITATIVE APPROACH TO PATIENT CARE IN GASTROENTEROLOGY—Edited by Thomas C. Chalmers, MD, Distinguished Physician, Boston Veterans Administration Medical Center; Lecturer and Member, Technology Assessment Group, Harvard School of Public Health, Boston; and President and Dean Emeritus, Mt Sinai Medical Center, New York. International University Press, The Old Ribbon Mill/Pitt St, Macclesfield Cheshire SK11 7PT, England, 1988. 214 pages, $49 plus $5 for postage and handling.

EMERGENCY CARDIAC MANEUVERS—A RESCUER'S HANDBOOK—Carl E. Bartecchi, MD, Clinical Professor, Department of Medicine, University of Colorado School of Medicine, Denver. Essential Medical Information Systems, Inc, PO Box 598, Amityville, NY 11701, 1989. 174 pages, $12.95 (paperback).

ENDOCRINE MANAGEMENT OF INFERTILITY—Edited by Terence J. Wilkin, Wellcome Senior Lecturer, Endocrine Section, Department of Medicine II, University of Southampton, UK. Harwood Academic Publishers, PO Box 786, Cooper Station, New York, NY 10276, 1988. 97 pages, $46 (paperback).

HANDBOOK OF BLOOD AND BLOOD PRODUCTS—S. Ghosh, Consultant, East of Scotland Blood Transfusion Service, Ninewells Hospital, Dundee, Scotland. MacMillan Press, distributed by Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1988. 114 pages, $19.95 (paperback).

INTENSIVE CARE—FACING THE CRITICAL CHOICES—Thomas A. Raffin, MD, Associate Professor and Assistant Chief of Medicine and Associate Director of the intensive care units, Stanford University Medical Center; Joel N. Shurkin, science writer, Stanford University News and Publications Service; and Wharton Sinkler III, MD, anesthesiologist and Episcopalian minister. W. H. Freeman and Company, 41 Madison Ave, New York, NY 10010, 1988. 204 pages, $14.95.

THE MANAGEMENT OF ANGINA PECTORIS—David L. H. Patterson, MD, FRCP, Consultant Physician and Cardiologist, Islington and Bloomsbury Health Authority, London. Castle House Publications Ltd, distributed by Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1987. 141 pages, $55.

MENOPAUSE: CLINICAL CONCEPTS—Steve London, MD, Director of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, and H. Jane Chihal, MD, PhD, Texas Endocrine and Fertility Institute, Carrollton, Texas. Essential Medical Information Systems, Inc, PO Box 598, Amityville, NY 11701, 1989. 142 pages, $12.95 (paperback).

ONCOGENES IN PEDIATRIC TUMORS—Edited by G. P. Tonini, L. Massimo, and P. Cornaglia-Ferraris, G. Gaslini Children's Hospital, Genoa, Italy. Harwood Academic Publishers, PO Box 786, Cooper Station, New York, NY 10276, 1988. 260 pages, $88.

PRACTICAL MANAGEMENT OF ISCHAEMIC HEART DISEASE—Graham Jackson, FRCP, Consultant Cardiologist, King's College Hospital, London. Distributed by Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1988. 225 pages, $55.

PREVENTING EMERGENCY MALPRACTICE—Raymond M. Fish, PhD, MD, Burnham City Hospital Trauma Center and University of Illinois, Urbana-Champaign, and Melvin E. Ehrhardt, MD, JD, Mennonite Hospital, Bloomington, Illinois. Medical Economics Books, Oradell, NJ 07649, 1989. 167 pages, $31.95.

PROBLEMS IN DERMATOLOGIC DIAGNOSIS & MANAGEMENT—Edited by W. Clark Lambert, MD, PhD, Associate Professor of Pathology and Dermatology; Director, Division of Dermatopathology, Department of Pathology; and Vice-Chairman, Division of Dermatology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark. American Academy of Dermatology, PO Box 3116, Evanston, IL 60204-3116, 1988. 266 pages, price not given.

RADIOPHARMACY AND RADIOPHARMACOLOGY YEARBOOK 3—Edited by Peter H. Cox, Rotterdam Radio-Therapeutic Institute, The Netherlands. Harwood Academic Publishers, PO Box 786, Cooper Station, New York, NY 10276, 1988. 329 pages, $145 (paperback).

Her anxiolytic is working—but she's alert, functioning, and at no risk of a benzodiazepine withdrawal syndrome when therapy ends.

BuSpar relieves anxiety and returns your patient to normal activity

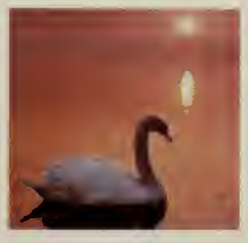
...with no more sedation (10%) than induced by placebo (9%)[1]
...without inducing significant cognitive[2] or functional impairment*
...without producing a benzodiazepine withdrawal syndrome[3] upon discontinuation

Effective choice for anxiety

BuSpar®

Tablets, 5 mg and 10 mg

(buspirone HCl)



for a different kind of calm

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

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MJL8-4225R2

BuSpar® (buspirone HCl)

References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986;80(3B):17-21 2. Luckhi, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987;23:207-211 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL 8-4225R2

Mead Johnson
PHARMACEUTICALS
A Bristol-Myers Company
Evansville, Indiana 47721

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

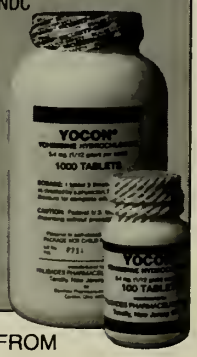
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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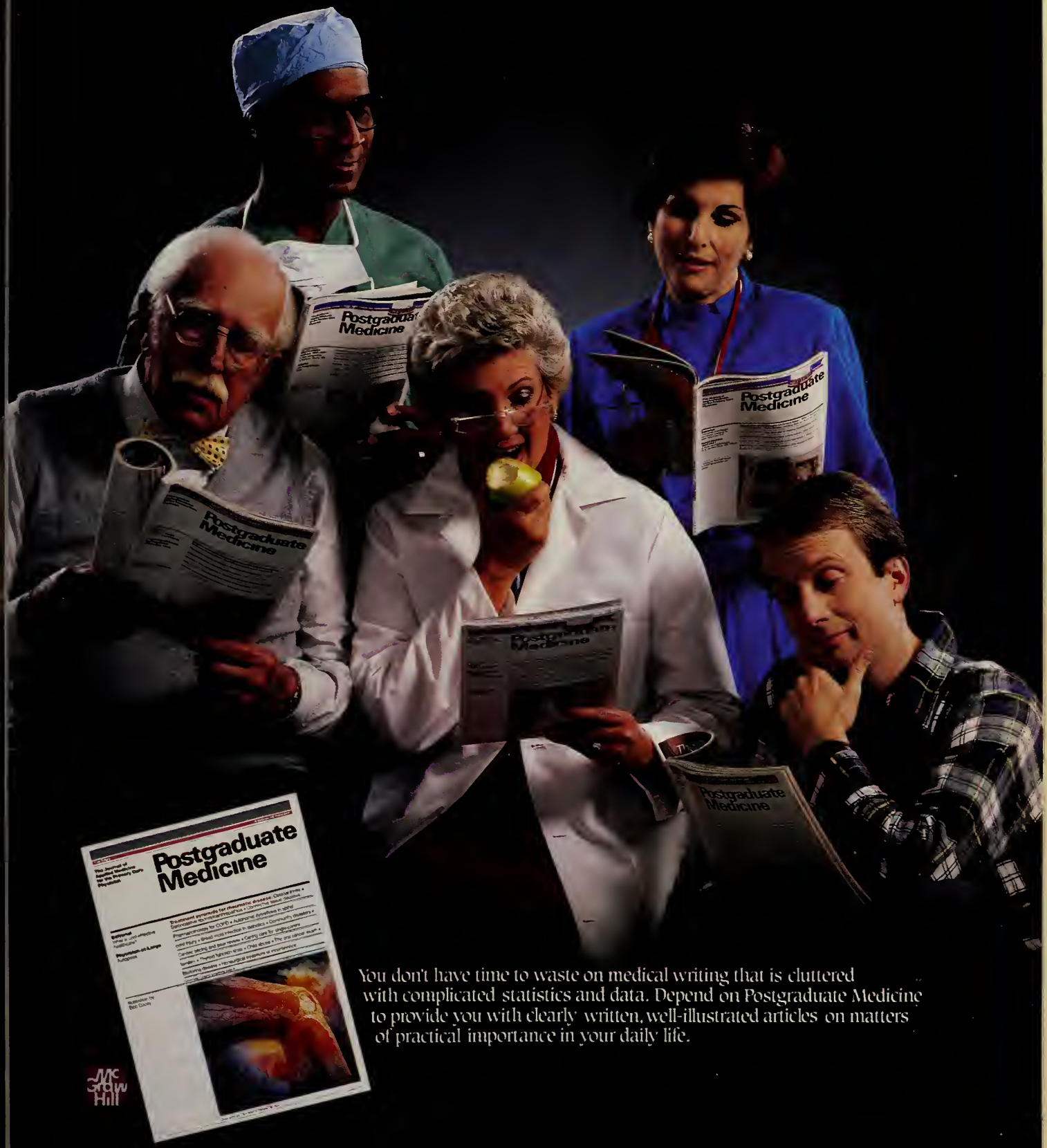

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BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumongenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE
There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:
1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987; 9(4):395-399

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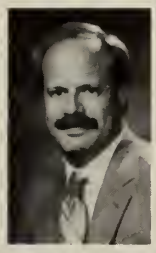
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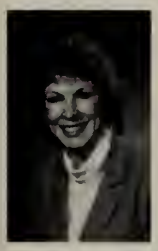
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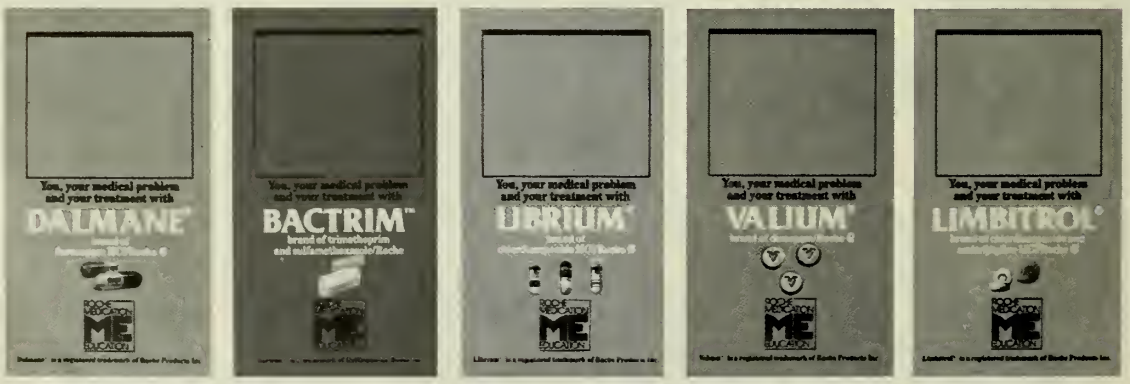
Because you are the primary source of medical information for your patients, we invite you to look over the Roche product booklets shown below. Ask your Roche representative for the new catalog brochure of patient education materials and for a complimentary supply of those booklets applicable to your practice.



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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 28-29—**Recent Advances in Cardiovascular Diseases.** The Registry Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

June 1—**1989 Arizona Medical Association Annual Meeting—Current Perspectives.** The Pointe at South Mountain. Thurs. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

April 15—**Selected Topics in Allergy.** UCLA at Los Angeles Airport Hyatt. Sat. 5 hrs. $30. Contact: UCLA.

July 21-22—**American In-Vitro Allergy/Immunology Society Annual Program.** American In-Vitro Allergy/Immunology Society at San Diego Marriott Hotel and Marina. Fri-Sat. 12 hrs. $200. Contact: Betty Kahler, PO Box 459, Lake Jackson, TX 77566. (409) 297-5636.

September 21-22—**Advances in the Diagnosis and Treatment of Allergic Diseases.** UCSF at Hyatt Union Square, San Francisco. Thurs-Fri. $200. Contact: UCSF.

ANESTHESIOLOGY

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

April 24-May 3—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn. 1½ weeks. 40 hours. $900. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Fisherman's Wharf. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 406)

CONTINUING MEDICAL EDUCATION

(Continued from Page 405)

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 23-24—**Advanced Cardiac Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

June 24—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

July 15—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: Deborah Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

June 2-3—**Southwestern Regional Cutaneous Flap Workshop.** UCLA Center for Health Sciences. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

June 25—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 16—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

April 26-28—**8th Annual Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Wed-Fri. 17 hrs. Contact: Orange County Trauma Society, 321 N Rampart, Ste 100, Orange 92668. (714) 937-5030.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 19-23—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 23-24—**Advanced Cardiac Life Support.** Center for Health Education at Long Beach. Fri-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 24-25—**11th Annual Poison Center Symposium: Emergency Medicine and Toxicology.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $280. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

April-June—**Seminars in Cytopathology 1989.** UCSF at Health Sciences Room 300. Thurs/monthly. 12 hrs. $140 full series/$30 single. Contact: UCSF.

(Continued on Page 408)

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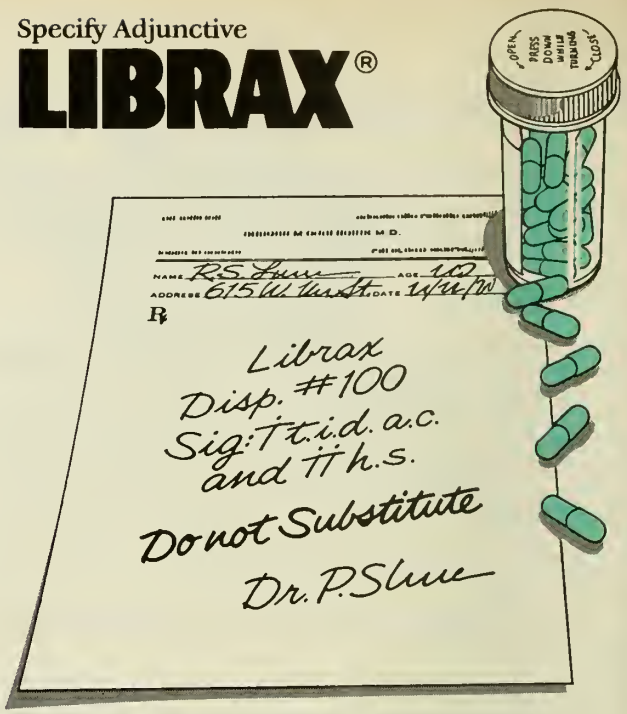

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

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In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

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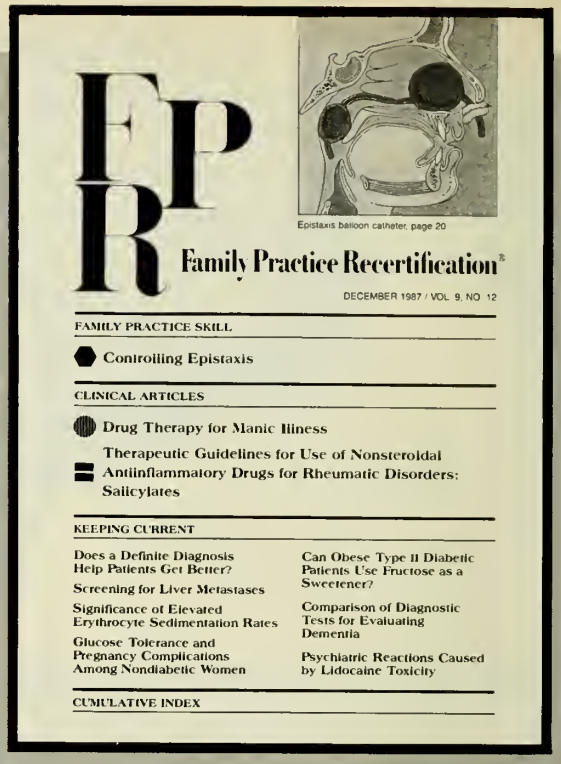
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(Continued from Page 406)

April 25-28—**Structural and Chemical Basis for Cell Function.** Annenberg Center for Health Sciences at Eisenhower. Tues-Fri. Contact: ACHS, 39000 Bob Hope Drive, Rancho Mirage 92270.

May 6-7—**Gastroenterology Update.** UCI. Sat-Sun. Contact: UCI.

May 6-13—**Internal Medicine.** STAN at Mauna Kea Beach Hotel, Hawaii. Sun-Fri. 25 hrs. $540. Contact: STAN.

May 21—**The California Tumor Tissue Registry's Semi-Annual Slide Seminar on Skin and Skin Appendage Tumors.** Sat. Contact: CTTR, 1200 N State St, Box 40, Los Angeles 90033. (213) 226-4614.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 14-16—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt Union Square. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

September 4-5—**International Conference on Thyroid Metabolism.** UCI at Queen Mary Hotel, Long Beach. Mon-Tues. Contact: UCI.

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

OB/GYN

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

June 30-July 4—**7th Annual Controversies in OB/GYN.** UCI at Mauna Kea, Hawaii. Fri-Tues. Contact: UCI.

July 29-August 8—**Update in Urogynecology.** UCI at Hawaii. 1 week/2 days. Contact: UCI.

OPHTHALMOLOGY

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

PEDIATRICS

April 14-16—**2nd Annual Pediatrics in Progress.** American Academy of Pediatrics at Las Vegas. Fri-Sun. 18 hrs. Contact: American Academy of Pediatrics, Dept of Education, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016 ext 7657.

April 15—**New Information on Old Exanthems.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Immunizations: Current and Future Vaccines.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 15—**Menstrual Problems in Adolescents.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

(Continued on Page 409)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 408)

April 15—**Common Presentations of Uncommon Conditions; Uncommon Presentations of Common Conditions.** Los Angeles Pediatric Society at Childrens Hospital, Los Angeles. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

April 27-28—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott. Thurs-Fri. Contact: UCI.

June 10—**Atherosclerosis; Pathogenesis and Screening.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Hypertension in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Office Evaluation of Sports Injuries.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Fitness Training in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 23-24—**Breastfeeding for Health Professionals.** UCSF at Hyatt Oakland International Airport. Fri-Sat. 10 hrs. $75. Contact: UCSF.

July 10-12—**Seminar for Physicians: Breastfeeding: A Natural World Resource.** La Leche League International at Anaheim Hilton and Towers. Mon-Wed. 16 hrs. Contact: LLLI, 9616 Minneapolis Ave, Franklin Park, IL 60131. (312) 455-7730.

July 18—**22nd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel Nob Hill, San Francisco. Thurs-Sat. 16 hrs. $275. Contact: UCSF.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

RADIOLOGY

April 16-21—**9th Annual San Diego Residents Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 28-30—**14th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

May 2-6—**9th Annual Mid-Pacific Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Royal Waikoloan Hotel, The Big Island of Hawaii. Tues-Sat. 19 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078

July 27-30—**3rd Annual Symposium on Magnetic Resonance Imaging.** Ritz-Carleton Resort Hotel, Laguna Niguel. Thurs-Sun. 23 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 30-August 3—**Napa Valley Imaging Update: MRI 1989.** UCD at Silverado Country Club, Napa Valley. Sun-Thurs. 17 hrs. $435. Contact: Nina Musselman, (916) 453-5390.

July 31-August 4—**Modern Radiology Practice.** UCSD at Four Seasons Biltmore Hotel, Santa Barbara. Mon-Fri. 24 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

April-October—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

(Continued on Page 413)

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(Enalapril Maleate-Hydrochlorothiazide|MSD)

- Favorable tolerability profile
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- Additive antihypertensive efficacy
- Once-a-day dosing

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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Tablets **Vaseretic** ONCE-A-DAY **ACE PLUS** INHIBITION

ACE [illegible]

Once-A-Day Vaseretic®

(Enalapril Maleate-Hydrochlorothiazide|MSD)

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: ***Hypotension:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*; ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

It hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS)

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema.* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy:* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release.* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents:* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium.* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium.* See WARNINGS, *Hydrochlorothiazide*; and PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide.*

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk; however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included. *Cardiovascular:* Syncope, orthostatic hypotension, palpitations, chest pain, tachycardia. *Gastrointestinal System:* Abdominal pain, vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous System:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, pruritus, decreased libido, rash, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN.* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*). *Gastrointestinal System:* Ileus, pancreatitis, hepatitis or cholestatic jaundice. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, rhinorrhea. *Other:* Photosensitivity, alopecia, flushing, taste alteration, glossitis. A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide—Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 3418—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

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CONTINUING MEDICAL EDUCATION

(Continued from Page 409)

May 6-13—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Hawaii. Sun-Fri. 25 hrs. $450. Contact: STAN.

May 20—**6th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic Surgery Medical Group at La Jolla Marriott Hotel. Mon. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

OF INTEREST TO ALL PHYSICIANS

April 19-21—**8th Annual Bright Horizons in Respiratory Care.** Annenberg Center for Health Sciences at Eisenhower. Wed-Fri. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270.

April 19-22—**4th International Symposium: Gyn/Onc/Surg/Urol.** UCI at Newport Beach Sheraton. Wed-Sat. 15 hrs. Contact: UCI.

April 26—**15th Annual Visiting Professor Program.** Saint Vincent Medical Center at Century Plaza Hotel, Los Angeles. Wed. Contact: Leah M. Nelson, (213) 484-5591.

April 29-30—**Clinical Strategies for the Primary Care Physician: Focus on the Aging Patient.** American Academy of Family Physicians Santa Clara at Monterey Conference Center Steinbeck Forum. Sat-Sun. 9 hrs. $150. Contact: Eugene Greider, MD, 877 Fremont Ave, Bldg J, Sunnyvale 94087. (408) 736-2304.

April 29-30—**The Cutting Edge 1989 Erotic Mysteries: Resolving Obstacles to Intimacy.** UCSD at San Diego Marriott Hotel & Marina. Sat-Sun. 12.5 hrs. $295. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 30-May 3—**12th Annual National Conference on Rural Health: Redesigning Rural Health: Blueprints for Success.** National Rural Health Association at Bally's Hotel, Reno, Nevada. Sun-Wed. Contact: Robert Quick, Communications Director. (816) 756-3140.

May 3-5—**10th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Stanford Court, San Francisco. Wed-Fri. $365. Contact: UCSF.

May 10—**Laboratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

May 13-14—**Controversial Diseases of the 80's.** UCLA at Hotel del Coronado, San Diego. Sat-Sun. 8 hrs. $145. Contact: UCLA.

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

May 25-26—**5th Annual Current Issues in Anatomic Pathology.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

June 1-2—**8th Annual Occupational and Environmental Medicine Symposium with Postgraduate Mini-Courses.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thurs-Fri. 17 hrs. $130. Contact: UCD.

June 4-9—**The Power of the Art: Humanism, Healing and Health Care.** Kauai Foundation for Continuing Education and The Hawaii Medical Association at Poipu Beach, Kauai. Sun-Fri. 25 hrs. $395. Contact: David J. Elpern, MD, 3420-B, Kuhio Highway, Lihue, HI 97666. (808) 245-5653.

June 11-16—**Family Practice Refresher Course.** UCI at Newport Beach Sheraton. Sun-Fri. 30 hrs. Contact: UCI.

June 23—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 28—**AIDS Update: Essential Issues in Primary Care Management.** Alta Bates-Herrick Hospital at Alta Bates Auditorium, Berkeley. Wed. 7 hrs. $75. Contact: Mary Grim, (415) 540-1420.

June 30-July 1—**Euthanasia: An Old/New Dilemma for Physicians.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

July 9-12—**3rd Annual Family Practice Board Review.** UCSD at Hanalei Hotel, San Diego. Sun-Wed. 20 hrs. $355. Contact: Janice R. Turner, PO Box 2528, La Jolla 92038. (619) 459-9597.

July 10-13—**Family Practice Board Review Course.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Thurs. 25 hrs. Contact: Division of Family and Community Medicine, 400 Parnassus Ave, A-C9, San Francisco 94143-0900. (415) 476-1482.

(Continued on Page 486)

TAGAMET® (brand of cimetidine)

See complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product.*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) Injection by intravenous bolus.*

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses, for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

How Supplied: Tablets: *200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).*

Liquid: *300 mg./5 mL., in 8 fl. oz. (237 mL.) amber glass bottles and in single-dose units (300 mg./5 mL.), in packages of 10 (intended for institutional use only).*

Injection:

Vials: *300 mg./2 mL. in single-dose vials, in packages of 10 and 30, and in 8 mL. multiple-dose vials, in packages of 10 and 25.*

Prefilled Syringes: *300 mg./2 mL. in single-dose prefilled disposable syringes.*

Single-Dose Premixed Plastic Containers: *300 mg. in 50 mL. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

ADD-Vantage®* Vials: *300 mg./2 mL. in single-dose ADD-Vantage® Vials, in packages of 25.*

'Tagamet' HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Baxter Healthcare Corporation, Deerfield, IL 60015.

**ADD-Vantage® is a trademark of Abbott Laboratories.*

8RS-TG:L788 *Date of issuance Aug. 1988*

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Before prescribing, please see brief summary of prescribing information on adjacent page

Journal of the Arizona Medical Association

ARIZONA MEDICINE

April 1989, VOL. XLVI, No. 4

Being Tired: The Real World

Marshall B. Block, M.D.

Ever since I was little, I remember my father saying to me, "Become a doctor, become a doctor!" It never occurred to me to ask how he knew what it was like to be a doctor. However, judging from my memory of what his days were like, a physician's life must have seemed to him like paradise.

His days lasted close to sixteen hours starting at 6 a.m. I still remember the smell of his aftershave lotion as he kissed me goodbye. He usually did not return until 8 or 9 o'clock in the evening. His days were not filled sitting at a desk or taking a two-hour lunch break or scanning a newspaper. Rather, they were tumultuous days consistently under pressure to get his work accomplished. His desk consisted of a stand on which a five line phone was constantly ringing and on which endless boxes and papers representing new and finished work was placed. Breakfast, lunch and dinner were brought in and eaten on the run, always standing, always during, between or after a major crisis was unfolding. The constant yelling between him and his workers and the pressures were the things most remembered whenever I visited him at his work place. Yet in an attempt to support our family, my father diversified his interests into real estate. It was at this endeavor that I remember and appreciate what "tired" must have really been like. Every Friday evening at 9 p.m., he would go to "collect rent." I, on occasion, accompanied him. It was not something that I enjoyed but felt compelled to do as it afforded him some time together with me. On the way to this task, my father occasionally pulled off the road and closed his eyes and fell asleep for fifteen to twenty minutes. I used to sit in the car watching him, not knowing what to do, but feeling quite sad at how hard he worked to help support us.

My father must have thought that our life as physicians was easier. Perhaps, in years past things were less chaotic, less organized, and less stressful but today things are different. Little did he know how hectic a physician's life can be. When describing his day, I thought about my day and then about some of my OB colleagues, and laughed. If we in medicine just had to heal, that would be enough. Now we are being placed under increasing scrutiny and pressure to perform both accurately and economically. My father's concern with accounts receivable, outstanding loans, payroll deadlines and insurance needs, seemed to him far removed from the practice of medicine. Today such is not the case. I suspect part of his reasoning to encourage my entry into medicine was to keep me out of his business. It is indeed amusing to think that my child must think the same when he sees me come home at night and fall asleep by 9 or 10 o'clock. Somehow though, my tiredness and that of my colleagues is different than the utter exhaustion that my father experienced. His was an exhaustion of survival. Thankfully, ours is an exhaustion of giving. It sounds somewhat corny but there is something special about being a physician, that makes being a doctor exciting, that makes the tiredness different and more acceptable.

Maybe he did know why it was special to be a physician after all. Whenever I am awakened at night with a phone call or I have to go to the Emergency Room to meet an ill patient, I think back and remember what "tired" was really like.

Marshall B. Block, M.D., Editor

Journal of the Arizona Medical Association

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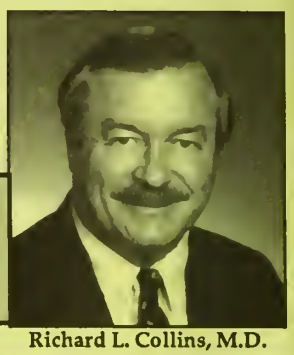
In This Issue:

-Are Doctors Next?
-Time Value of Money
-Viewpoint
-Microbiology-Immunology
-New Members
-Magnetic Resonance
-Classified Ads

From Our President



Richard L. Collins, M.D.

ArMA physicians who have been through the lawsuit system and personally know its pressures and problems have formed a support group to help colleagues facing the same trauma. When your vasovagal response subsides and the malpractice lawsuit papers are still on your desk, you should know you don't have to face the isolating, demoralizing litigation experience alone.

ArMA's Peer Support Committee has been established to provide emotional support and technical information to help both you and your spouse cope with the litigation process, which has been known to tear families apart as well as demoralize individuals.

Volunteer contact persons throughout the state will refer you to an appropriate committee member who will:

❑ **Help you handle stress**: Many physicians experience serious interpersonal problems as a result of litigation-related pressures. The support group can help you focus on what's really important in your life instead of letting stress damage personal or professional relationships.

❑ **Provide technical information**: Committee members who have been through the lawsuit system can offer practical advice on preparing. They can tell you what is important and share the hazards of common mistakes which can hurt you in court.

❑ **Bolster your self-confidence**: A malpractice lawsuit can deplete self-confidence essential for your credibility in court. The support group can help put your problem in perspective so you are not your own enemy while testifying.

If you need help—or if you know someone else who does—help is as close as your telephone. Please call one of the Physician Support Committee volunteer contact persons listed below who can then connect you with an appropriate counselor who will help you deal with the stress and problems associated with the lawsuit process.

The volunteer contact persons are:

Gilbert Sechrist, M.D., Flagstaff — 774-1811
William J. Mangold, Jr., M.D., Tucson — 297-8381
J. Frank Martin, M.D., Yuma — 344-1400
Joseph W. Hanss, Jr., M.D., Phoenix — 258-3262

Being sued for malpractice is one of the most traumatic events which any physician has to face. Knowing that others have had to face the same process, and knowing that they survived and are willing to talk about it can help any of us cope with our own crisis.

We are not alone. And you don't have to be. ■

Richard L. Collins, M.D.

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..... Are Doctors Next?

Professional practice marketers are not Board Certified, but the few good ones are on a "Board" all their own.

By Richard C. Thompson

First it was the attorneys. Then the accountants decided it was their turn. The dentists were not going to be upstaged so they wanted in too. Could the doctors be the next group to get with it? With what? The "M" word. Marketing. You know, business development. Practice development. There are a lot of names for it, but the objective is always the same: more patients and more revenues.

Trends in marketing have matured significantly over the last 10 years in all industries with the advent of computer technology. Today, introducing a new product or service to the consumer is serious business and can be as sophisticated as the space shuttle. The high cost of an unsuccessful marketing effort can have devastating effects on corporate image and the corporate kitty. But successful marketing efforts will continue to produce more customers, more income, bigger pension plans, more toys to play with and for some, an earlier retirement.

The consumer is far and away more informed than ever before. It's frightening to think about patients in your office talking about MetLife's $100 million pretax loss on HMOs this year and by the way, doctor, "Do you think they will really lose $500 million before they can turn it around?" This increased awareness and trend of being a good medical consumer is not going to go away. It's going to accelerate and the smart physicians will be rewarded handsomely for their insight and ability in taking advantage of these opportunities.

The trends in professional practice marketing are changing rapidly as well. Business development for the professional practice has been percolating over the last 5 years and is now coming of age. The legal profession has embraced this change and is taking definitive steps towards building their practices. The accounting profession is learning quickly that when the referral network stops, so does this year's bonus, pension plan funding, or the new office equipment and car. The dental profession appears to be caught in between this new philosophy and the way it's been done before; the necessity of building a practice with time-tested marketing vehicles and being a dentist is all that it takes and the patients will come in by the busload. Marketing is the most popular seminar that the American Dental Association offers; however, many dentists still believe that advertising and marketing "cheapens" the profession.

In 1986, the legal profession started a group called NALFMA, the National Association of Law Firm Marketing Administrators. It's a trade association for those people who try to generate new business for our nation's law firms. The association was founded with a national membership of 40. Their population now is close to 400.

The accountants don't have such a trade organization yet; however, the trends towards increased marketing activity, especially for Arizona firms, are quite interesting. In a survey of Arizona accounting firms conducted by a major Texas public accounting group, there have been significant advances in marketing and business development activity. The accountants appear to be going about it the correct way too--methodically, precisely, and thoroughly.

The Texas survey points out that more and more Arizona firms are starting their marketing efforts with a written marketing plan. In 1987, only 9.1% of the Arizona accounting firms who responded to the Texas survey indicated that they had a written marketing plan. Just one year later, 14.3% had a written marketing plan done. Overall, media advertising and developing brochures are down. Good solid planning and attention to detail is up. Even marketing training for the Arizona accounting firm's professional staff went

from 0% in 1987 to over 14% in 1988 in the same survey. Now, that's the way to do it.

The most common question going around professional practices is, "Can I advertise (do marketing) without compromising my professional image?" The answer is always the same and without reservation...yes. A good business development campaign will always enhance or embellish the firm's professional image. The campaign is always done in accordance with the written marketing plan which should provide a detailed picture of the market that the practice is trying to do business in. The plan will have already determined the basic sensitivities and dynamics of the marketplace. Only a "cheap" marketing effort will "cheapen" the profession.

So what are some of the keys to starting a good business development plan and how do you select someone to help build your practice? Here are some things that have had a high success rate:

1. Remember that your practice is also a business. You must treat it like a business if you want it to grow. Your attitude must reflect this business concept.

2. The competition for medical care will not go away. When the Arizona economy turns around and the migratory inflow of people improves, the competition for the health care dollar will increase like never before. The time to begin a business development plan is now. You must make a conscious effort every day to improve your ability to get more patients into your office.

3. Seek competent business development advice. Unless you are current in the legal and technical ways of proper marketing techniques, get (at least) a second opinion.

4. A truly professional and competent business development practitioner should be well rounded and have some experience in business start-ups and turn-arounds. This means that the person you choose needs to know how to run a business. They need to know about finance and should feel comfortable with your accountant (if need be) and business office manager as well. The outstanding practitioners are highly computer literate.

5. Their experience is key. Ideally, they should have both corporate marketing experience and advertising agency experience. Since these two worlds are totally separate, having both types of experience will be of benefit to you.

6. Ask a potential practitioner what elements should be in a good marketing plan (the correct answer is corporate goals & objectives, market demographics, strategy and tactical issues, budgets, and timelines).

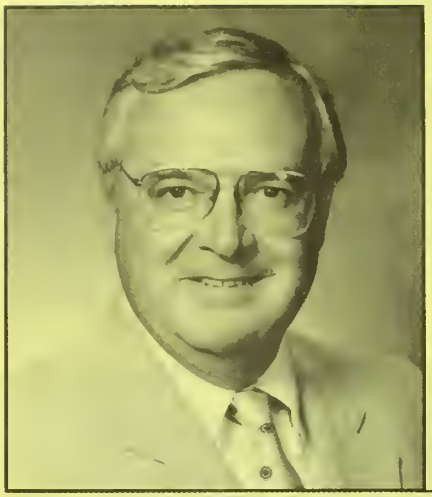
7. Always ask for a list of professional references.

8. Avoid practitioners who only want short-term involvement with your practice. A good business development plan comes with a written document and four quarterly reviews.

9. A good practitioner will interview you just like you with them. They should ask questions that you have never thought about before.

10. Remember, the only way things get better is when you get better....and smarter.

Mr. Thompson is President and CEO of RTA, Incorporated, an Irvine, California firm specializing in business development for the professional practice. Their current clients include CPA and accounting firms, attorneys, dentists, and financial planners in Southern California and Arizona. Mr. Thompson is frequently published in the insurance industry, financial planning industry, has been a featured speaker with the Direct Marketing Association in New York, the American Society of Woman Accountants, and has held senior management positions in advertising agencies and management positions in Fortune 100 companies. In addition to Mr. Thompson's current responsibilities, he serves as chief investment advisor for four private trusts in Orange County, California. His address: RTA, Inc., 18 Terracima, Irvine, California, 92720. (714) 559-5032.



Dick Pearson

Time Value of Money

With the phasing in of lower marginal income tax brackets at the federal level, many of our members are asking us whether it makes any sense to defer income when most experts expect tax rates to go back up in the future. This argument has particular relevance to deferred compensation plans, where many members assumed a lower post-retirement tax bracket would provide tax savings.

Since the expectation is that a post-retirement bracket will likely be higher than the 28/33% maximums today, why should any one opt to defer income now?

The answer lies in the understanding of the concept known as "Time Value of Money." The principles of Time Value of Money (hereinafter TVM), are that it is better to save a dollar today, and pay a dollar tomorrow.

This idea is not simply based on mathematics; it is a psychological feeling that motivates people to save on their taxes TODAY. Most people don't really care how much they will save ten or twenty years from now, most of us are still reeling from last April's surprise. We are worried about the bill coming due this April. But we are not going to worry as much about a tax due at age 65, when that time is far off. This is the psychology behind the once-popular leveraged real estate syndications, with heavy up front tax write-offs. There was a taxable gain to be paid somewhere down the road, but the investor did not care as long as he/she saw the write-offs NOW.

It is this same psychology that motivates people to defer income now, and be willing to pay a potentially higher tax later. A conceptual way to express this psychology is: "What is the present value of a tax due many years from now?" This tax has to be discounted by the fact that it has been deferred for so long.

Perhaps an example will demonstrate the point:

Assume you are facing a decision on whether to defer the receipt of $100,000 of income this year by depositing it into a deferred compensation.

Your choices are to receive it as taxable income now, or take the risk of a higher rate when you take the money out at retirement.

Your federal tax bracket is 28%--your age is 40--retirement age is 65. We assume that in 25 years, the period of deferral, the top marginal bracket is 50%, and that you are in that bracket.

We'll also assume an investment rate of return of 8%, after tax, and an inflation (discount) rate of 6%.

Let's measure, in present value terms, the net present value of deferring the $100,000 (the deferral plan) as opposed to receiving the money as taxable income now (the cash plan). We do this by calculating the future value of the after-tax investment, and then reduce that figure to today's money. We'll also chart the present value effect of the 50% tax to be paid in 25 years (discounted by a 6% inflation factor, that tax in today's money is 11.65%).

Given the parameters of this scenario, the point at which deferral makes sense is for 10 or more years. Of course, this assumes that even after five years deferral your marginal rate is 50% (possible, but not probable); and that the difference between the investment rate of return and inflation stays at 2%; and that you actually deposit the after-tax cash in a tax sheltered vehicle (such as life insurance). Finally we have assumed that you are currently in a 20% tax bracket. Many of you facing this choice are in a 33% penalty bracket.

The results of this analysis are compounded many times over if successive annual deposits are made until retirement. Suffice it to say that most people will continue to defer income today if it will save taxes today. The fact that a tax must be paid someday is discounted in the mind by the psychological factor reduced to a TVM mathematical analysis demonstrated here.

The ArMA Membership Benefit Trust, which is an ideal way to fund for severance benefits, malpractice tail insurance premiums, protect assets from creditors, and to supplement your retirement plan on a **Tax Deductible** basis is an excellent vehicle in its own right. When the time value of money principal is factored into the equation it is even more attractive.

DEFERRAL PLAN		CASH PLAN
$100,000	Gross investment	$100,000
0	Current tax	(28,000)
$100,000	Net Investment	**$72,000**
$159,560	Net Future Value (NFV) year 25	$114,890
18,590	Present Value Future Tax (11.65%)	0
$140,970	After Tax Future Value	**$114,890**
$ 26,080	Net Value of Deferral	

*NFV reflects the future value of $100,000 invested at 8% over 25 years, discounted by inflation of 6% over 25 years.
You may be wondering what the result looks like if a shorter deferral period is used.

$122,670	At Net Future Value (NFV) year 20 (pv deferred tax=15.59%)	$104,640
$104,750	AT NFV, year 15 (pv deferred tax=20.86%)	$ 95,300
$ 86,890	AT NFV, year 10 (pv deferred tax=27.92%)	$ 86,800
$ 68,780	AT NFV, year 5 (pv deferred tax=37.36%)	$ 79,050

Please call me at the ArMA office to find out how the Trust can benefit you.

Dick Pearson
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Third and Fourth Person Sharing a Cabin: $1,094.00 Each
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Join Us July 1-July 8

Viewpoint:

By John Hudson, Principal, Barry Goldwater High School, and Chair, State Select Commission on Adolescent Suicide

The National Institute of Mental Health estimates for every high school of two thousand or more students in the United States there is at least one successful suicide and between thirty and fifty attempts each year. There are statistics and studies to fill volumes--all telling us the same thing: suicide among the young is a problem which has been steadily growing and shows no signs of going away.

In Arizona (ranked second nationally for rate of suicide), suicide is the second leading cause of death for young people between the ages of 13 and 19. These facts present a tremendous challenge for our schools and all individuals who deal with adolescents. The difficult questions are those which ask what should the role of the school, the teacher, the school counselor and nurse be. Hopefully, it will be that of provider of prevention education as well as intervention strategies.

"Suicide among the young is a problem which has been steadily growing and shows no signs of going away."

When these topics are discussed people often ask, "Is growing up today so different from when other generations grew up?" I believe so. Consider the following: In our country today, 17% of the school-age children live in a "traditional" family setting. This is where one parent works and one stays home to parent. In contrast to this, 22% live in family settings where the adults live out of wedlock. Furthermore, 21% live in family settings where both parents work.

Less and less time is being spent in meaningful family communication. Numerous studies have suggested that the family spends only 14 minutes per week in one on one focused uninterrupted communication with their children. When we consider this we must ask ourselves where our young people are learning their values, problem-solving skills, decision-making skills and basic social skills. The answer seems to be from the media and from their friends. The age at which the average young person's friends are exerting as much influence over them as that of their parents is 10 years old.

The role of schools needs to change to include more and more of what I call the human curriculum. As part of the curriculum of courses such as health, human relations, family living, child development, psychology and sociology, we must integrate units on communication, dealing with stress, depression, relationships, death and dying, and specifically suicide.

Schools need to concentrate on teaching certain skills for living in the elementary grades. We must help young people feel good about themselves and possess the skills necessary to become healthy adolescents. Middle and junior high schools must focus on the reinforcement of these skills and the teaching of peer resistance in order to face the challenges of drugs, alcohol and other self-destructive behaviors. Finally, our high schools must support positive peer leadership programs and realize that intervention programs such as peer counseling, mediation training, support group, etc., are necessary if we are to help our young people make it through adolescence.

John Hudson

Reprinted courtesy of "Governor's Office For Children"

New Directions In Microbiology and Immunology

The immune response of a normal individual is a complex and precisely regulated set of events beginning with recognition of " non-self" by cellular receptors that culminates in the production of effector T cells (e.g. killer cells) or circulating antibodies. Specific antibodies, in the presence of serum complement, can destroy invading cells or pathogens. Key areas of recent progress that should serve as guideposts for continued studies for the next decade are T cell recognition of antigens, the "lymphokine revolution," immunology and cancer, developmental pathways of lymphocyte differentiation and the search for new and improved vaccines.

Thymus derived lymphocytes (T Cells) are of fundamental importance to the immune response because, through their unique immunoglobulin-like receptors (a/B or y/B heterodimers), they can recognize foreign pathogens, virally infected cells and tumor antigens and can differentiate into regulatory cells that augment later phases of the immune system (helper or amplifier T cells) such as antibody production or the generation of cytoxic killer T cells. Moreover, under certain conditions T cells can become suppressors that down regulate or shut off the development of an immune response. Furthermore, T cells can themselves undergo neoplastic transformation becoming leukemias, and a surface marker (CD4) expressed on the surface of human helper T cells serves as a target or attack by human immunodeficiency virus (HIV) considered to be the causative agent of AIDS. The a/B heterodimer is found on those helper and cytotoxic T cells that see antigen in the context in the major histocompatability complex (MHC). The presentation of fragments of protein antigens, by MHC products themselves expressed by B cells to T cell receptors is an area undergoing extensive investigation.

The nature of the receptor for antigen on antigen-specific suppressor T cells is problematic at this time. Considerable effort is being expended to understand the nature of this receptor and also of the soluble antigen-specific molecules produced by suppressor T cells that function in shutting off the normal immune response. These factors may also serve to ameliorate destruction by T cells in autoimmune diseases, and to play a role in suppressing the maternal immune response to the growing fetus, which serves as a natural allograft.

Only ten years ago, there was a sense of magic associated with the growth of immune cells in culture. Nossal (Immunology Today, 9, 286-291, 1988) points out that the growth of understanding in this area in the last few years has been so great, that it should be considered a revolution, the "Lymphokine Revolution." Since 1980, seven molecules known to regulate communication among immunocytes (interleukins) have been molecularly cloned and are available for investigation and clinical use. In addition, five other hemopoietic growth regulators and molecules such as tumor necrosis factor, gamma interferon, transforming growth factor B (TGFB) and other molecules that show profound modulating effects on the immune system are now available for investigation. In some cases, the activities of these molecules is not restricted to the immune system but the molecules will cross-stimulate with cells of the nervous system. One clinical application of the lymphokine revolution has been the development of LAK cells that are generated by treatment with interleukin-2 (IL-2) and will serve as effective killers of certain tumors.

Based upon our increasing knowledge of tumor specific surface antigens exhibited by cancers such as melanomas, neuroblastomas and fibrosarconomas, coupled with increasing information regarding lymphokine function and the increasing sophistication in the production of monoclonal (hybridoma) antibodies. It can be expected that immune response modifiers and immunotoxins (toxic molecules coupled to antibodies) will find an important place in the treatment of cancer.

The most practical application of immunology has always been that of vaccination. This area has been remarkably successful with the eradication of smallpox, diphtheria, and many other classically known infectious diseases. However, not all infectious diseases respond satisfactorily to available vaccines. These include parasitic diseases such as malaria, mycoses such as Valley Fever and other diseases like Whooping Cough where optimal vaccines have yet to be developed although the causative agent is known. The cause of AIDS, human immunodeficiency disease virus (HIV), is a prime example of the latter. Considerable knowledge of HIV gene structure is available, and new approaches involving sophisticated peptide chemistry and recombinant DNA technology are being used to predict portions of the viral envelope that are antigenic and might prove to be worthwhile as vaccines. This virus is uncooperative to such approaches because it varies its antigens from generation to generation, a phenomenon which thus far has precluded direct development of vaccines. In the case of tumor antigens, very few of these molecules have been characterized at the protein or gene level so the development of synthetic or recombinant vaccines must wait. In this area, an anti-idiotype approach, using antibodies directed against the combining site of the anti-tumor antibody has proven useful in experimental systems.

Immunology has emerged as a strong and productive discipline that is based upon classical microbiology and infectious disease treatment and research. The role of cells and molecules of the immune system in normal growth, development and aging and in the development and elimination of a variety of disease conditions is fundamental. Continued basic and clinical research into this area is essential. Modern immunology is broadly based and retains its place at the bedside as well as gaining from and contributing to modern biochemistry and molecular biology.

John J. Marchalonis, Ph.D.
Professor and Head
Department of Microbiology and Immunology

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Shreveport - 1982

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Otorhinolaryngology
5251 W. Campbell, Suite 110
Phoenix
University of Minnesota
Medical School-
Minneapolis - 1983

Robert L. Allen, M.D.
Ophthalmology
3333 E. Camelback Road
Suite 122, Phoenix
Loyola University of Chicago-
Stritch School of
Medicine - 1945

John K. Bradway, M.D.
Orthopedic Surgery
333 E. Virginia, Suite 118
Phoenix
University of Arizona
College of Medicine - 1983

David M. Creech, M.D.
Plastic Surgery
604 W. Warner Road, Suite D-1
Chandler
University of Missouri-
Columbia School of
Medicine - 1981

Donni L. Fleischaker, M.D.
Pediatrics
11209 N. Tatum Boulevard
Suite 150, Phoenix
University of Oklahoma
College of Medicine - 1981

Gordon F. Genta, M.D.
Otorhinolaryngology, Allergy
2600 E. Southern Avenue
Suite J-2, Tempe
University of Utah
College of Medicine - 1978

Robert A. Marlow, M.D.
Family Practice
7301 E. 4th Street
Suite 22, Scottsdale
University of Colorado
School of Medicine - 1974

Stephen J. McGirr, M.D.
Neurological Surgery
13400 E. Shea Boulevard
Scottsdale
Baylor College of
Medicine - 1982

Ira H. Ungar, M.D.
Emergency Medicine
820 E. Circle Road, Phoenix
Faculty of Medicine University
Autonoma de
Guadalajara - 1974

Associate

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Joseph H. Reno, M.D.
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621 West Beal, Flagstaff
Temple University School of
Medicine-Philadelphia - 1941

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216 W. Echo Lane, Phoenix
State University of New York
College of Medicine-
Syracuse - 1954

Bernard Krasner, M.D.
General Surgery
25150 N. Windy Walk Drive
Unit 52, Scottsdale
Tufts University School of
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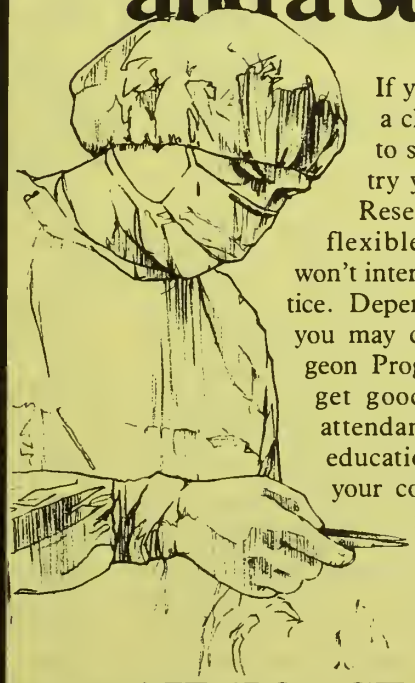

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Reducing the Volume of Ineffective Medicare Services

The American Society of Internal Medicine has developed a four-part action plan on how to reduce ineffective Medicare services. The plan includes increased data collection, more effective medical review, reform of the physician payment system, and development of appropriate practice guidelines.

Little is known about the real reasons for the increase in the volume of services to Medicare beneficiaries. Much of the increase may not reflect ineffective or unnecessary services at all, but better medical care. Yet the need to reduce the number of ineffective Medicare services--whatever the reason--is paramount.

Between 1975 and 1987, Medicare outlays increased at an average annual rate of 15.5 percent. This year the Medicare program will cost $97 billion, and it is estimated by the Health Care Financing Administration (HCFA) that expenditures will increase by an additional $10 billion in 1990. Overall, the Medicare program accounts for more than 8 percent of the federal budget. Given these budget increases, as well as the projected increases in the Medicare population that will continue to expand budgetary pressures, public policy is needed for ensuring that beneficiaries receive appropriate care and that the expenditures for Medicare go only toward those services that are truly effective.

A major factor contributing to these increases in Medicare outlays is the volume of Medicare services, defined as the number of services rendered per Medicare beneficiary during a defined period of time. Under Medicare Part B, where expenses have increased by an average 18 percent a year between 1975 and 1986, more than 40 percent of the increase was attributable to increases in the volume of services. Since physicians' practice patterns influence more than 70 percent of all medical services, special efforts need to be made to ensure that medical services are appropriately utilized. These practice patterns need to be carefully studied since at this point little is known on whether the increase in the volume of services can be attributed to better medical care, lack of knowledge or consensus on the effectiveness of various medical interventions, the shift of services from hospitals to outpatient settings or other factors.

As an initial step, the Department of Health and Human Services (HHS), in close cooperation with the medical community, should increase its data collection and analysis of these different practice patterns and later use this information in formulating approaches to reform physician payment, enhance medical review and develop practice guidelines. Medical providers and policy-makers currently cannot make sound judgments about slowing increases in medical care costs until they know what is effective, appropriate medical care. The American Society of Internal Medicine (ASIM) believes there are several projects and initiatives, such as combining the Medicare data files and examining practice variations, that will increase the medical community's understanding of practice patterns and enable it to effectively limit the use of inappropriate medical services.

Medical review by both federal peer review organizations (PROs) and Medicare carriers is another potentially effective tool for assuring the proper utilization of Medicare services. Recent changes to these programs, as required by Congress, have expanded both the level of review and, consequently, those programs' role in assuring the appropriate use of services. ASIM believes the effectiveness of these programs, however, can be further enhanced if the programs are modified to include more active medical participation, better criteria and screens and more focused review.

A third option for assuring that the number of services provided to beneficiaries is appropriate is to reform the physician payment system. Different health policy analysts have suggested a range of options, from establishing a fee schedule based on a resource-based relative value scale (RBRVS) to creating a capitated payment system (through the use of managed care systems or expenditure targets) to developing a preferred provider organization (PPO) that would use only "efficient" practitioners. Of these different options, the RBRVS is the most attractive approach for both preserving beneficiaries'choice of (and access to) a wide variety of practitioners while simultaneously helping to control the volume and cost of medical services. Specifically, an RBRVS would create a payment fee schedule based on the resource costs of providing those services, thereby eliminating some of the per-

verse incentives under the current system to overutilize well-compensated services and underutilize marginally reimbursed services, such as cognitive or primary care services.

A fourth option for controlling the volume of inappropriate medical services is to influence medical practice patterns through the development of practice protocols. Recent studies clearly have indicated that wide variations in practice patterns have resulted in differences in the quality of patient care, patient outcomes and the cost effectiveness of beneficiaries' care. To address this issue, Congress had held preliminary hearings on the efficacy of establishing practice guidelines, and the Physician Payment Review Commission (PPRC) sponsored a conference to explore how practice guidelines may be developed and used. The Society supports the study and development of practice guidelines but also believes that the medical community must be intricately involved in the process in order for the guidelines to be effective.

Although these all are viable options for comprehensively addressing the increase in medical volume, there is no easy method for solving this problem. Rather, the medical community, Congress, the administration and the PPRC all need to work cooperatively at this issue by developing clinically sound yet effective ways for ensuring that Medicare is covering only necessary and effective services.

The rate of increase in Medicare Part B services and the limited federal budget make it incumbent upon the medical profession to provide effective yet clinically sound methods for limiting ineffective Medicare services. In many areas, research is needed so that judgments can be made for determining the cost-effectiveness of medical care without detracting from beneficiaries' health care. The recommendations included in the ASIM action plan provide comprehensive directions so that not only the medical community but also Congress and the administration can develop methods for both controlling the Medicare budget and enhancing the cost effectiveness and quality of beneficiaries' health care. To do this effectively, however, Congress and the administration will need to support programs for increasing data collection and analysis, developing more effective medical review, reforming physician payment and creating appropriate practice guidelines.

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Through the Adult Family Care program, homes and caregivers are carefully screened and monitored by the Foundation. The program is designed to provide homes for those among Arizona's elderly population who can no longer live independently but who do not need expensive nursing home care. The Foundation's goal is to maximize the potential for senior adults to retain control over their own lives.

Adult Family Care sponsors receive assistance in meeting all county requirements, free training in home care (first aid, nutrition, medication management and personal care techniques), monthly payments, emotional support and additional assistance as needed.

For more information about receiving care in an Adult Family Care home, call Maricopa County's long-term care eligibility office, (602) 262-8788. To become an Adult Family Care sponsor, call the Foundation for Senior Living, (602) 274-3600.

Prescott Physicians Die

Clarence Edgar (Ned) Yount, Jr., M.D., a lifelong Prescott resident and second generation practicing physician, followed his wife, **Florence B. Yount, M.D.**, into death at the beginning of this year. Dr. Florence Yount, an obstetrician and pediatrician, died at the end of 1988.

"Dr. Ned," as he was known to friends, a general practitioner, surgeon and anesthesiologist, was born December 7, 1905, in a house on the corner of Marina and Gurley Streets, now the site of the Hassayampa Inn. After graduating from George Washington University Medical School in Washington, D.C., he returned home to Prescott to join his father, C.E. Yount, Sr., M.D., in general medical practice.

He was joined later in practice by his bride, "Dr. Florence," a former fellow medical student at George Washington University who had gone to Chicago to complete her pediatrics residency at the Illinois Children's Hospital following their 1936 wedding at her family home in Iowa.

Together, they provided Prescott's residents with more than four decades of medical care. Following service in the South Pacific in WWII, when Dr. Florence was one of the few physicians left to provide medical care in the community, Dr. Ned returned to Prescott and became very involved in public health. He served as the city/county health officer and in 1938 was instrumental in initiating smallpox vaccinations for all public school children, a very controversial issue then.

Dr. Florence delivered a significant percentage of the babies born in Prescott, and then delivered many of their children. She continued to care for the children she delivered in a well baby clinic she initiated.

Both doctors were very active in the community: he as a member of the Yavapai County Sheriff's Jeep Posse, the Westerner's Club, the Kiwanis, and the Aztlan Masonic Lodge No. 1; and she as a senior elder of Prescott Community Church, a local historian, and member of the Mountain Artists Guild and Alta Vista Garden Club. Both were members of the American and Arizona Medical Associations and the Yavapai County Medical Society. The Younts are survived by their son, John Edward Yount of Prescott, and two granddaughters.

Dear Doctor:

There is an urgent need for medical professionals to alert young males ages 20-35 about testicular self-examination.

Although, as you are aware, this is a relatively rare disease, it is also a totally treatable one to cure, if diagnosed in its earliest stages. Much as females have benefited from breast self-examination and from routine pap smears, young men may also benefit if they are properly informed about this disease and educated in self-examination.

This age group of young men usually does not present any other health problems and are no longer seen by pediatricians for routine care. Therefore information must be easily accessible for them with printed material in college and university health centers, in mall medical clinics, as well as doctor's offices and perhaps via broadcast media, medical problems.

The catastrophic results of leaving testicular cancer untreated is not news to medical professionals. It is news to most of the public who has never heard of the disease, and its process of being multiple tumors which spread rapidly.

Our son was in college when his left lung collapsed. The x-ray showed one tumor blocking the air passage, others appeared on the lungs, back and abdomen. The source was found in the testicle. He thought his right testicle was shrinking: while the left one was growing. He did not know . . . it was abnormal! The symptom was there--he was not knowledgeable.

As concerned parents who have lived through the nightmare of our son's Stage III testicular carcinoma, radical surgery and chemotherapy, we strongly urge that you address this devastating health menace and help educate our young men about their bodies and the implications of this disease. The public looks to you, the medical profession, for information about early detection and treatment of all health problems.

Please make testicular education a priority and move with speed on a program for this special need. An excellent folder, Testicular Self Examination by NCI, NIH Publication #87-2636 is available by calling 1-800-4-CANCER.

Most Sincerely,
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Cholesterol Monograph Available

A continuing medical education independent study monograph on cholesterol is available free of charge to individual physicians and CME directors from the National Cholesterol Education program of the National Heart, Lung and Blood Institute of the National Institutes of Health (HIH).

The monograph, *Cholesterol: Current Concepts for Clinicians,* is targeted for the physician in practice who wants to update knowledge of the latest treatment guidelines issued by the program and who is genuinely interested in the opportunity to obtain two hours of category I credit prior to October, 1989. Credits are awarded through Hahnemann University upon successful completion of a quiz which accompanies the monograph.

The monograph is important because it is an update of the earlier version issued in 1987 and contains new information based on the report of the Adult Treatment Panel of the National Cholesterol Education Program. Its contents include:

- Coronary heart disease: evidence for the role of blood cholesterol
- Lipid metabolism and hypercholesterolemia
- Classification of patients by total and LDL-cholesterol
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- Drug treatment
- The importance of a multidisciplinary team approach

Copies of the monograph may be requested from:

National Cholesterol Education Program -- Box CME, 4733 Bethesda Avenue, Suite 530, Bethesda, MD 20814.

MRI Offers Winning Edge In Sports Medicine

A state-of-the-art diagnostic procedure called Magnetic Resonance Imaging (MRI) is now returning injured athletes to the playing field much sooner and without the pain of diagnostic surgery.

For one Phoenix Cardinal football player, MRI proved useful in defining what a clinical evaluation couldn't determine, according to John Omohundro, head athletic trainer for the Phoenix Cardinals. Had the player not passed the physical, he wouldn't have been qualified to play for the Cardinals.

"The standard clinical exam required of all new players showed some wear on the surface of the player's knee," said Omohundro. "But further examination by MRI showed there was no degeneration of the knee, and the player signed with the Cardinals."

MRI, hailed as the most significant discovery in diagnostic medicine since the x-ray, has been used since 1982 to pinpoint disorders of the head and central nervous system.

But medical experts now consider MRI superior in many cases to x-rays, CT and arthrograms in diagnosing torn knee cartilages, runner's knee, shin splints, herniated disk, tennis elbow and other sports injuries, according to Rolf Vrla, M.D., a radiologist at Valley MRI in Phoenix who has participated in research projects testing the accuracy of MRI in orthopedic knee applications.

"MRI shows every structure in the knee," said Vrla. "With other imaging modalities, there are only a few things you can look at with any accuracy. And in some cases, we are even finding that MRI can provide an even clearer view of the problem area than the surgeon's scope."

The technology is offered in the Tucson area at Tucson Medical Center, University Medical Center, Carondelet St. Mary's Hospital and at Tucson Imaging Associates, a physician-owned health center. In northern Arizona, MRI technology is available at Flagstaff Medical Center. In Central Arizona, MRI services are provided by Walter O. Boswell Memorial Hospital, Sun City; Scottsdale Memorial Hospital, Scottsdale; and in Phoenix at Good Samaritan Hospital & Medical Center, St. Joseph's Hospital & Medical Center, Valley MRI and Thunderbird MRI. Valley and Thunderbird MRI centers are operated by TME, Inc.

"MRI is unique because it is the most sensitive noninvasive method of producing clear images of the ligaments, tendons, and cartilage, where most sports injuries occur," said Kirk Bucon, M.D., director of MRI at Valley MRI and Thunderbird MRI. "X-ray produces clear images of bones, but poor images of the tissues surrounding the bone. Arthroscopy provides direct visualization of the tissue, but unlike MRI, it is an invasive, surgical procedure."

Arthroscopy is one of the most common methods of diagnosing problems associated with runner's knee and other sports-related injuries, but MRI is diminishing the number of diagnostic arthroscopies as the initial modality of choice, according to Bucon.

"Injuries to the knee are common for both weekend and professional athletes, yet the knee traditionally has been one of the more difficult areas of the body to image," said Bucon. "For example, there are actually some blind spots in the knee with the arthroscope that MRI shows in detail. MRI creates clearer images of the tissue surrounding the knee and ankle as well and the Achilles tendon--areas that are susceptible to sports-related injuries."

Even when surgery is necessary, most physicians agree that MRI also can lead the way to the specific problem much faster and more effectively than other imaging modalities, resulting sometimes in lower medical costs.

"MRI can provide valuable information for the orthopedic surgeon planning to perform arthroscopic surgery," said Vrla. "MRI can localize abnormalities before surgery, allowing the surgeon to correct the problem without having to spend time finding the problem."

According to Cherrill Farnsworth, chairman of TME, Inc., TME research shows that more MRI scans are being conducted today than ever before and an average of about 20 percent of the scans are related to sports injuries. *

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Clinical Investigation

Glycosylated Hemoglobin Measured by Affinity Chromatography in Diabetic and Nondiabetic Patients on Long-term Dialysis Therapy

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We measured by affinity chromatography glycosylated hemoglobin levels in the blood of 43 diabetic and nondiabetic patients (139 measurements) on long-term dialysis therapy (continuous ambulatory peritoneal dialysis and hemodialysis) to determine the usefulness of this method of estimating glycemic control in diabetic persons on dialysis therapy. In nondiabetic patients, glycosylated hemoglobin levels were within the normal range (4.0% to 6.8% of total blood hemoglobin levels) for both continuous ambulatory peritoneal dialysis and hemodialysis. Glycosylated hemoglobin values correlated significantly with fasting blood glucose levels, serum urea levels, and serum total carbon dioxide content. By stepwise regression, fasting blood glucose values accounted statistically for .54 of the variability (R^2) in glycosylated hemoglobin. The contribution of the other variables to this variability was minimal. In 9 diabetic patients (3 on hemodialysis), glycosylated hemoglobin levels correlated significantly with average daily blood glucose levels. Regression of the fasting blood glucose value on glycosylated hemoglobin was similar between continuous ambulatory peritoneal dialysis and hemodialysis. Measuring glycosylated hemoglobin levels by affinity chromatography is a suitable method for assessing glycemia in dialysis patients.

(Tzamaloukas AH, Hsi KC, Quintana BJ, et al: Glycosylated hemoglobin measured by affinity chromatography in diabetic and nondiabetic patients on long-term dialysis therapy. West J Med 1989 Apr; 150:415-419)

We did this prospective study to determine whether glycosylated hemoglobin (hemoglobin [Hb] A_1) levels, measured by affinity chromatography, are appropriate for assessing glycemic control in diabetic patients on dialysis treatment. Nonenzymatic glycosylation of hemoglobin A posttranslation results in the four fractions, A_{1a1}, A_{1a2}, A_{1b}, and A_{1c}, that make up HbA_1.[1] The percent of HbA_1 in blood is proportional to the integrated blood glucose concentration.[1] Therefore, HbA_1 levels are measured to assess the control of glycemia in patients with diabetes mellitus.[1] In azotemic persons, HbA_1 measured by cation-exchange chromatography does not correlate with blood glucose levels because of interference of carbamylated hemoglobin with the assay of HbA_1.[2,3] Carbamylated hemoglobin is produced by a condensation of urea-derived isocyanic acid with the *N*-terminal amino groups of globin.[2] The use of HbA_1 levels as a measure of glycemia in patients with uremia has also been questioned for other reasons.[3,4] Nondiabetic patients with uremia have impaired glucose tolerance.[5] Uremia also shortens the life span of erythrocytes, and hemolysis decreases HbA_1 levels.[6] Finally, many uremic patients receive frequent transfusions of erythrocytes containing different concentrations of glycosylated hemoglobin.

Because a normal blood glucose level remains a desirable goal in diabetic persons on dialysis therapy,[7] a reliable indicator of integrated glycemia would be valuable in the care of these patients. Carbamylated hemoglobin does not interfere with the measurement of HbA_1 by affinity chromatography.[8] Certain questions regarding the appropriateness of affinity chromatography for HbA_1 determination in dialysis patients remain unanswered. This study addresses the following specific questions: Are HbA_1 levels normal in nondiabetic persons receiving dialysis? and Is glycemia the only blood measurement in dialysis patients statistically affecting HbA_1 levels? In clinical studies, significant correlations between HbA_1 levels and the degree of azotemia[8] and between HbA_1 levels and the degree of uremic acidosis[9] have been reported. Yet, glycosylation of hemoglobin is the same in azotemic and nonazotemic environments in vitro.[10]

Patients and Methods

The hemoglobin A_1 concentration was determined in fasting venous blood specimens of 43 patients on long-term dialysis therapy—two to four determinations per patient—over a period of six months. In the same blood specimens, a fasting blood glucose level, serum urea concentration, serum creatinine concentration, and serum total carbon dioxide (CO_2) content were also determined.

We studied four groups of patients: patients with diabetes on continuous ambulatory peritoneal dialysis (CAPD)

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ABBREVIATIONS USED IN TEXT

CAPD = continuous ambulatory peritoneal dialysis
Hb = hemoglobin

therapy (n = 9), diabetic persons on hemodialysis therapy (n = 8), nondiabetic persons on CAPD therapy (n = 11), and nondiabetic persons on hemodialysis therapy (n = 15). Of the 17 patients included in the diabetic groups, 16 had long-standing diabetes mellitus, either insulin-dependent or non-insulin-dependent; renal failure due to diabetic glomerulosclerosis, with typical clinical features; and one or more other end-organ manifestations of diabetes (retinopathy, 16 [100%]; neuropathy before renal failure, 16; gastroparesis, 12 [75%]; leg gangrene, 2 [13%]). In one patient with renal failure due to complications of nephrolithiasis, clinically overt diabetes developed several months after the initiation of hemodialysis, and this patient was included in the diabetic group on hemodialysis. This patient and one other diabetic person on hemodialysis therapy were not receiving insulin. All other diabetic patients on hemodialysis therapy and all diabetic patients on CAPD therapy were taking insulin during the study period.

The nondiabetic groups included patients with renal failure of diverse causes. The most common causes of renal failure were glomerulopathies and nephrosclerosis. Patients in the nondiabetic groups met two criteria: no past history of diabetes determined by reviewing clinical records and by patient interview, and fasting blood glucose levels that were consistently below 7.8 mmol per liter[7,11] after dialysis therapy was started. Postprandial blood glucose levels were not used as a criterion for ruling out diabetes, as they are difficult to interpret in uremic patients.[7] Three nondiabetic patients in the CAPD group and three in the hemodialysis group were classified as having impaired glucose tolerance by repeated fasting blood glucose levels between 6.4 and 7.8 mmol per liter.[7,11] Three of these patients had conditions known to be associated with impaired glucose tolerance, including advanced hepatic cirrhosis, pancreatic insufficiency, and a recent intake of corticosteroids.

A blood hemoglobin concentration was determined simultaneously with an HbA_1 measurement. The record of each patient in this study was reviewed for blood transfusions during the six months of the study and the four months before it. In contrast to patients on CAPD therapy, hemodialysis patients are not in a steady state of serum urea and creatinine concentrations and total CO_2 content. Therefore, for hemodialysis patients, postdialysis serum concentrations of these three variables were also determined. Time-averaged concentrations were then computed[12] and were included in the statistical analysis.

Hemoglobin A_1 levels were measured by boronate-affinity-gel column chromatography.[13(pp805-806)] The columns were manufactured by Endocrine Sciences, Tarzana, California. For the measurement, blood collected in ethylenediaminetetraacetic acid tubes was hemolyzed by adding deionized water, and a portion of the hemolysate was loaded on a column. The column was then washed with a buffer containing ammonium acetate, magnesium chloride, and sodium azide to remove the nonglycosylated hemoglobin and the rapid fractions of the glycosylated hemoglobin. A second buffer containing sorbitol was then applied to elute the HbA_1 from the column. The total hemoglobin level and the HbA_1 fraction were quantitated by absorbance at 414 nm in a Gilford spectrophotometer. Hemoglobin A_1 levels are reported as percentages of the total hemoglobin concentration in blood. Fasting blood glucose levels, serum urea and creatinine concentrations, and total CO_2 content were determined by a Beckman Astra-8 analyzer.

We computed the correlation between HbA_1 levels and the other named variables by pairs. Each measurement was taken to represent one data point (measurements = 139). When we did the same analysis using each patient's average as one data point (n = 43), the results were similar. The fasting blood glucose level may be a poor measure of integrated glycemia. Nine diabetic patients (six on CAPD therapy) had repeated blood glucose determinations (fasting and postprandial) during the days of drawing blood specimens for the HbA_1 assay. For these patients, we computed average daily glucose concentrations and compared them to HbA_1 levels. Between four and six blood specimens daily were needed for computing one average daily blood glucose level. The number of days averaged for one determination was between one and five with the days of the HbA_1 concentration in the middle if more than two days were averaged. Between one and four pairs of average daily blood glucose and HbA_1 values were available per patient (total 26).

Further statistical analysis was done on the interrelations of the five fasting variables. Initially the frequency distributions of these variables were examined by "stem-and-leaf" and "box" plots. By these methods, the frequency distributions were shown to be not normal, and one blood glucose level and four serum urea concentrations were identified as outliers. These findings indicate departures of the data distribution from statistical assumptions necessary for linear-regression models. The departures were corrected to a degree by logarithmic transformation of the variables and by omitting from the statistical analysis the observations identified as outliers. The logarithmically transformed variables were then entered in the stepwise-regression procedure[14] to search for the independent variables that have a high degree of regressive relation with HbA_1 levels.

Finally, we compared the regressions of blood glucose values on HbA_1 levels between patients receiving CAPD and hemodialysis patients. The rationale for this comparison was

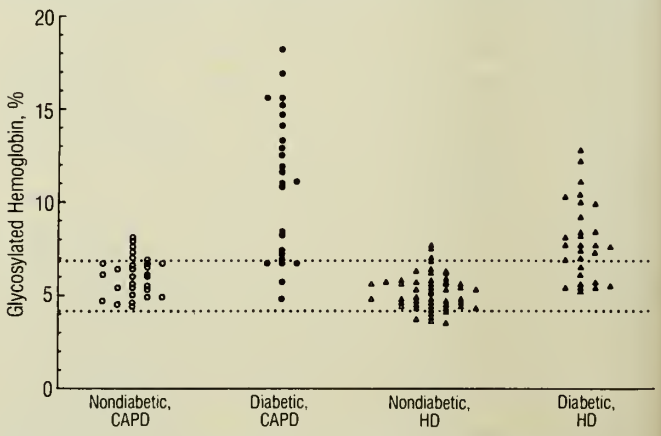

Figure 1.—The graph shows glycosylated hemoglobin levels in nondiabetic and diabetic patients on either continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis (HD). Multiple (2 to 4) measurements for each patient are shown (n = 139). Interrupted lines show the upper and lower normal limits for the assay. For nondiabetic patients, CAPD measurements were statistically higher than hemodialysis measurements ($P < .005$, 2-tailed nonpaired t test).

that CAPD and hemodialysis therapy represent different states of both glucose metabolism—because patients on CAPD are never in a true fasting state—and azotemia and acidosis—because patients on hemodialysis therapy are not in a steady state for either of these two clinical conditions.

Results

Figure 1 shows glycosylated hemoglobin percentages in the four groups studied. Normal values for HbA_1 in this laboratory are between 4.0% and 6.8%. For nondiabetic patients on CAPD therapy, 95% confidence limits of HbA_1 were 5.5% and 6.8%. Few measurements were greater than 6.8%. All these measurements were from patients with impaired glucose tolerance. For nondiabetic patients receiving hemodialysis, 95% confidence limits for HbA_1 were 4.9% and 5.5%. Few measurements exceeded 6.8%, and all were obtained from patients with impaired glucose tolerance. Hemoglobin A_1 measurements were greater than 6.8% in 81% of the specimens from diabetic patients on CAPD therapy and in 68% of the specimens from diabetic patients receiving hemodialysis.

Table 1 shows the initial (beginning of the study) and final (after six months) blood hemoglobin concentrations. Blood hemoglobin levels remained stable in all four groups. Transfusions of packed red cells (two units each) were administered during the study period to one nondiabetic patient on CAPD therapy and two nondiabetic patients and one diabetic patient on hemodialysis therapy. In the four months before the study, no transfusions were administered. An external loss of blood or preparing for transplantation were the indications for transfusion in three of the four transfused patients.

Table 2 shows fasting blood glucose levels, serum urea and creatinine concentrations, and total CO_2 content that were determined simultaneously with the glycosylated hemoglobin levels. For hemodialysis patients, serum urea, creatinine, and CO_2 concentrations are time-averaged. Statistical differences between the four groups are noted in the table. Table 3 shows the correlation matrix between HbA_1 levels and the other four variables. With the exception of the serum creatinine levels, all the "independent" variables correlated significantly with HbA_1 values. The fasting blood glucose level showed the highest correlation by far. Of note is the high degree of intercorrelation between the "independent" variables of blood glucose, creatinine, urea, and total CO_2 content. Figure 2 shows a linear regression between the fasting blood glucose and HbA_1 levels. To avoid superimposing many symbols, only the average of each patient is plotted. Linear regression with each pair of measurements providing one data point (n = 139) reveals essentially the same results. The correlation between daily average blood glucose and HbA_1 levels was .8732 (n = 26; $P < .01$). For the same 26 determinations of HbA_1, the correlation between the fasting blood glucose and HbA_1 levels was .7141 ($P < .01$)

TABLE 1.—*Initial and Final (After 6 Months) Blood Hemoglobin Concentration**

	Peritoneal Dialysis		Hemodialysis	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
Initial				
Range	66-119	80-130	56-125	54-104
Mean±SD	100±17	107±17	84±19	80±16
Final				
Range	62-126	83-135	62-135	57-110
Mean±SD	103±19	107±18	87±21	80±17
P†	NS	NS	NS	NS

NS=not significant, SD=standard deviation

*Grams per liter.
†Two-tailed, paired *t* test.

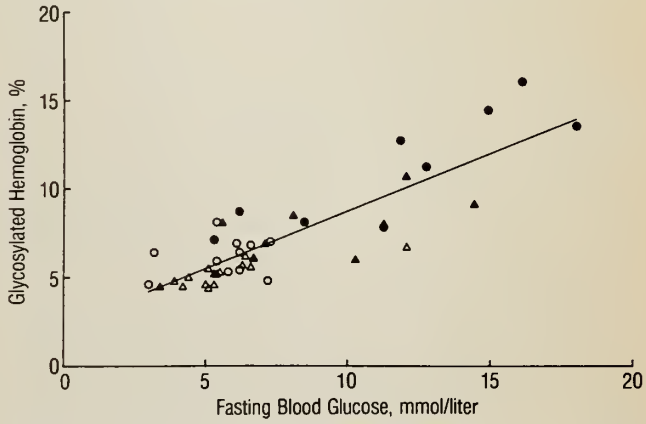

Figure 2.—The graph shows the linear regression of fasting blood glucose levels on glycosylated hemoglobin levels. The average for each patient is plotted (n = 43) (Y = 2.29 + 0.64X; r = .847 [$P < .01$]). ○ = nondiabetic patients on continuous ambulatory peritoneal dialysis (CAPD) treatment, ● = diabetic patients on CAPD therapy, △ = nondiabetic patients on hemodialysis, ▲ = diabetic patients on hemodialysis

TABLE 2.—*Serum Concentrations Measured Concomitantly With Hemoglobin A_1 Determinations**

Patient Group/Therapy		Fasting Glucose, mmol/liter	Urea, mmol/liter	Creatinine, μmol/liter	Total Carbon Dioxide, mmol/liter
Nondiabetic/CAPD	Range	2.6-10.4	12.0-31.5	470-1,570	19.0-26.0
	Mean±SD	5.7±1.8	22.0±6.0	910±340	22.4±2.6
Diabetic/CAPD	Range	3.9-30.1	11.0-31.0	380-1,110	19.0-27.0
	Mean±SD	10.8±6.2	19.0±5.0	660±230	23.1±2.4
Nondiabetic/hemodialysis	Range	2.9-12.6	8.0-31.0	430-1,010	13.5-23.0
	Mean±SD	4.9±0.8	24.0±5.0	690±170	18.4±2.1
Diabetic/hemodialysis	Range	3.7-17.8	18.0-29.0	480-1,140	16.5-23.0
	Mean±SD	9.3±3.3	23.0±3.0	670±170	20.0±1.8
Normal values	Range	3.3-5.9	3.5-7.0	50-110	22.0-27.0

SD=standard deviation

*Statistically significant differences of the means (2-tailed, nonpaired *t* test) are as follows: **A**, within each dialysis modality (nondiabetic to diabetic): fasting blood glucose, continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis, both at $P < .001$; urea, CAPD, $P < .05$; and creatinine, CAPD, $P < .005$. **B**, between dialysis modalities (CAPD to hemodialysis): total CO_2, all patients, $P < .001$; fasting blood glucose, only nondiabetic groups, $P < .01$.

TABLE 3.—*Correlating Matrix Between Glycosylated Hemoglobin Levels, Fasting Blood Glucose Levels, Serum Urea and Serum Creatinine Concentrations, and Serum Total Carbon Dioxide Content (n=139)*

		Blood Glucose	Serum Urea	Serum Creatinine	Total CO_2
Hemoglobin A_1,	*r*	.712	−.374	−.091	.315
	P	<.001	<.001	.285	.002
Blood glucose,	*r*		−.264	−.181	.242
	P		.002	.033	.004
Serum urea,	*r*			.402	−.516
	P			<.001	<.001
Serum creatinine,	*r*				−.046
	P				.589

and between the fasting blood glucose and average daily blood glucose levels was .7702 ($P<.01$).

The presence of the intercorrelations between the "independent" fasting variables made the use of the stepwise-regression procedure necessary. After logarithmic transformation of the data, four variables were shown to be related to the HbA_1 value in a statistically significant way. These were the fasting blood glucose and serum urea and creatinine levels and an interaction factor between the blood glucose and serum urea levels. Combined, these factors accounted statistically for .60 of the variability (R^2) in HbA_1 levels. The fasting blood glucose value alone accounted for .54 of this variability. A regression analysis was done three times including all the data after logarithmic transformation; excluding the outliers and with logarithmic transformation; and excluding the outliers, excluding the serum urea, and with logarithmic transformation. This analysis yielded essentially similar results. The R^2 remained around .60 in each analysis. The contribution of the fasting blood glucose level to this variability was around .50 in each analysis.

A comparison of the regression lines of the blood glucose on the HbA_1 value between CAPD and hemodialysis patients revealed that neither the regression coefficients nor the Y intercepts differed statistically between the dialysis populations.

Discussion

A tight control of blood glucose levels in diabetic patients on dialysis therapy may prevent a rapid acceleration of atherosclerosis[7] and a progression of microvascular complications.[15] Physicians and patients often do not estimate glycemic control accurately.[16,17] A reliable method of estimating HbA_1 levels in diabetic patients on dialysis therapy would have clinical use.

Chromatography is the most commonly used method of measuring HbA_1 levels. Carbamylated hemoglobin has similar negative electrical charges as some of the fractions of HbA_1 and cannot, therefore, be separated from HbA_1 by cation-exchange chromatography.[2,9,15,18-23] Affinity chromatography, which has been included among the chromatographic methods considered unsuitable for determining HbA_1 levels in uremic subjects,[3] does not measure carbamylated hemoglobin as part of the HbA_1. The affinity chromatographic column contains diimidazole-activated agar matrix to which aminophenylboronic acid is coupled. The HbA_1 is separated by a coupling of the boronate of the column with the glucose molecules that are attached to the globin moiety of HbA_1.[24,25] Several studies have shown agreement between HbA_1 measurements by boronate affinity chromatography and other indicators of glycemia in dialysis patients but raised the questions addressed by this study.[8,26,27]

The findings of this study are as follows:

- Hemoglobin A_1 levels are normal in nondiabetic persons on dialysis therapy.
- The statistically significant negative correlation between HbA_1 levels and the degree of azotemia and the positive correlation between HbA_1 levels and the total CO_2 content were due almost entirely to the statistical interactions between fasting blood glucose and serum urea levels and between the blood glucose levels and total CO_2 content.
- The indexes of glycemia correlated strongly with HbA_1 levels and accounted largely for their variability.

The normality of HbA_1 levels in nondiabetic persons on dialysis therapy can be the result of either normal blood glucose levels or a combination of uremic hemolysis, which decreases HbA_1 levels, and uremic glucose intolerance, which increases HbA_1 levels. Uremic glucose intolerance, however, is corrected to a great extent by adequate dialysis.[28] Furthermore, the finding that blood hemoglobin levels remained constant in this study with minimal amounts of transfusions militates against an accelerated rate of erythrocyte destruction. Although the question is not completely answered, our evidence suggests that the normal HbA_1 levels in nondiabetic patients receiving dialysis do not result from a combination of uremic hemolysis and uremic glucose intolerance.

The correlations between fasting blood glucose levels and the variables indicating azotemia and acidosis reflect the fact that for diabetic patients, dialysis therapy is started earlier than for nondiabetic patients,[29] and they have, consequently, lower serum urea and higher serum CO_2 levels (Table 2). The small but independent effect of the serum creatinine value on the statistical variability of HbA_1 levels found in the stepwise-regression procedure reflects in part the earlier initiation of dialysis therapy in diabetic patients and the debilitated state often present in diabetic patients on dialysis therapy.[30]

Finally, the process of glycosylation appears to be similar between CAPD and hemodialysis, despite dissimilarities in availabilities of glucose (continuous versus intermittent), in acid-base control, and in the control of azotemia. As expected, both fasting blood glucose and HbA_1 levels were higher in patients receiving CAPD than in those receiving hemodialysis. Yet the regression of blood glucose levels on HbA_1 levels did not differ between the two treatments. These findings are consistent with the hypothesis that glycemia is the only important variable in HbA_1 formation in dialysis patients. In vitro findings are also consistent with this hypothesis.[10]

We suggest that HbA_1 levels should be measured by affinity chromatography in persons on dialysis therapy when there is doubt about glucose control and routinely in diabetic patients at infrequent intervals—for example, every six months. This method also provides an objective means of assessing glycemic control when specific interventions are studied, as when the intraperitoneal administration of insulin is compared with subcutaneous insulin for blood glucose control of diabetic patients on CAPD therapy.

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Diuretic-Induced Gout

WE ARE SEEING SOMETHING NEW IN GOUT that is very interesting—it is called diuretic-induced gout. We are finding this in a population over the age of 70, as opposed to the usual gout sufferer, who is usually about 40. We are seeing women more commonly than men, which is a total reverse.

These patients have acute attacks, frequently in the hands and knees. Basically, these are elderly women on diuretics with Heberden's or Bouchard's nodes, coming in with some tophaceous deposits in these little osteoarthritic changes in the hands, and this is so-called diuretic-induced gout. Many times these patients have mild renal insufficiency, and it is something you want to think about. They come in with this acute inflammatory process in their hands. If they have osteoarthritis, but it looks too inflammatory for mere osteoarthritis or even an erosive osteoarthritis, think about diuretic-induced gout.

—STEVEN R. WEINER, MD

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Acute Myocardial Infarction and Sudden Death in Sioux Indians

SHARON L. HRABOVSKY, *Pittsburgh;* THOMAS K. WELTY, MD, MPH, *Rapid City, South Dakota; and* JOHN L. COULEHAN, MD, MPH, *Pittsburgh*

While some Indian tribes have low rates of acute myocardial infarction, Northern Plains Indians, including the Sioux, have rates of morbidity and mortality from acute myocardial infarction higher than those reported for the United States population in general. In a review of diagnosed cases of acute myocardial infarction over a 3-year period in 2 hospitals serving predominantly Sioux Indians, 8% of cases were found misclassified, and 22% failed to meet rigorous diagnostic criteria, although the patients did indeed have ischemic heart disease. Patients had high frequencies of complications and risk factors and a fatality rate of 16% within a month of admission. Sudden deaths likely due to ischemic heart disease but in persons not diagnosed as having acute myocardial infarction by chart review occurred 3 times more frequently than deaths occurring within a month of clinical diagnosis.

(Hrabovsky SL, Welty TK, Coulehan JL, et al: Acute myocardial infarction and sudden death in Sioux Indians. West J Med 1989 Apr; 150:420-422)

From 1981 to 1983, the total age-adjusted cardiovascular mortality rate among American Indians and Alaskan Natives was 192.3 per 100,000, 19% lower than that of the United States population as a whole (238.3 per 100,000), with a 30% lower mortality rate from ischemic heart disease.[1] Moreover, the rate of morbidity from diagnosed acute myocardial infarction (MI) from 1982 to 1984 was only about 40% of that reported for the US population (1.2 versus 2.9 hospital discharges per 1,000 persons).[1] These averages, however, conceal variations in cardiovascular morbidity and mortality among different Indian groups. Historically, southwestern Indians have had low rates of cardiovascular disease, documented by both prospective and retrospective studies.[2-10] Other tribes have been less well investigated, but a report by Pinkerton and Badke indicated that Crow and Northern Cheyenne Indians of Montana had rates of coronary heart disease approximating those found in the Framingham study.[11] Death certificate and hospital discharge data from the Aberdeen (South Dakota) and Billings (Montana) Indian Health Service areas (which serve Northern Plains Indians) indicate cardiovascular morbidity and mortality rates more than three times higher than those of Navajo Indians.[1] Cardiovascular mortality for 1982 to 1984 in the Aberdeen area was 351.7 per 100,000 compared with 103.3 per 100,000 in the Navajo area.

The purpose of this study was to ascertain morbidity and mortality from acute MI among a defined population of Sioux Indians using rigorous diagnostic criteria; to assess the contribution of sudden death to cardiovascular mortality; and to determine the clinical characteristics, complications, and outcome of acute myocardial infarction in this population.

Patients and Methods

Rosebud and Rapid City Indian Health Service (IHS) hospitals each serve a geographically defined population of Indians (predominantly Sioux) in western South Dakota. In 1985 the population of the Rapid City Indian community was 4,421 and that of the Rosebud Reservation was 8,618. Both hospitals are small, acute care facilities providing primary inpatient care for patients with acute MI. For more specialized services, such as cardiac catheterization and the treatment of unstable arrhythmias, patients are referred to non-IHS hospitals under contract arrangements.

We reviewed the inpatient charts of all Indians discharged with a primary diagnosis of acute MI or other ischemic heart disease during a three-year period (fiscal years 1983 through 1985) from Rosebud and Rapid City IHS hospitals and their contract facilities. Diagnostic criteria were the same as those used in previous reports of acute MI among Navajos.[9,10] In brief, a confirmation of acute MI required serial electrocardiographic changes of ST segment elevation with late T wave inversion and evolution on serial tracings, including the appearance of Q waves 0.04 seconds or more in duration; or the described ST and T wave changes associated with characteristic serial elevations of creatine kinase levels. If Q waves were absent but creatine kinase confirmation present, a subendocardial (non-Q wave) infarction was diagnosed. After reaching a final diagnosis for each patient, we abstracted information from the chart concerning complications during the hospital stay, clinical features, outcome, and associated conditions or risk factors.

We also reviewed death certificates for the four South Dakota counties—Todd, Mellette, Tripp, and Pennington—in

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ABBREVIATIONS USED IN TEXT
IHS = Indian Health Service
MI = myocardial infarction

which both Rapid City and the Rosebud Reservation are located to ascertain "sudden deaths" of Indians not diagnosed as having acute MI during the three-year period. "Sudden death" was defined as death due to a presumed cardiac cause occurring within an hour of symptoms or collapse as ascertained from the notation on the death certificate (underlying causes of death, ICD-9* codes 410 to 414, 427.5, 428.0, or 429.2).[12(p13)] This included Indians who were dead on arrival at emergency services, who died in emergency departments before being admitted, or who died in nursing homes or while patients at non-IHS hospitals. Such sudden deaths were presumed to be caused by either an acute MI or primary ventricular fibrillation and were considered part of the ischemic heart disease mortality.

Results

Diagnosing Acute Myocardial Infarction

In all, 98 patients were discharged from the two hospitals with a diagnosis of acute MI during the three years. Of these, 94 (96%) hospital charts were found and abstracted, and 64 (68%) were confirmed by our criteria as having sustained an acute MI. Another 29 (31%) had been misdiagnosed as having acute MI, and 1 patient fit into the category of sudden death. Of the 29 misdiagnosed cases, 21 patients (72%) had other evidence of chronic ischemic heart disease or angina, although they did not have sufficient documentation of acute MI during the index hospital admission. The other eight misclassified cases (28%) were found to have clinical diagnoses of pulmonary embolus, right bundle branch block, alcoholic cardiomyopathy, alcoholic liver disease, neonatal asphyxia, and chronic obstructive lung disease. While many of the former group may have failed to meet our criteria because of poor documentation on the chart, the latter group was clearly misclassified because of coding errors.

If one includes all 98 patients indicated by hospital discharge diagnosis as having had an acute MI, the annual discharge rate for this disorder in this population was 2.50 per 1,000 persons. This is consistent with the age-adjusted discharge rate reported for the entire Aberdeen IHS area (1982 to 1984) of 2.76 per 1,000 persons.[1] The morbidity rate based on chart review is 1.66 per 1,000 if only the 64 confirmed cases and 1 sudden death are included, or 2.30 per 1,000 if the additional 21 cases of ischemic heart disease are included as true cases of acute MI.

Although the rates of confirmed acute MI are lower in Sioux women than in Sioux men, this advantage is primarily in the premenopausal age group (Table 1).[13] Elderly Sioux women appear to have acute myocardial infarction more frequently than elderly men. It is diagnosed about as frequently among Sioux men as among men in the Framingham cohort, although the Framingham rates are based not only on clinical events but on biennial examination of all participants (Table 1). Sioux women have higher rates of acute MI than Framingham women. While the occurrence of acute MI among Navajo Indians is increasing, Sioux men are still 3½ times and Sioux women 6½ times more likely to be diagnosed as having an acute MI.

Clinical Characteristics

Of 64 documented acute myocardial infarctions, 12 (19%) were anterior, anteroseptal, or anterolateral in location; 22 (34%) were inferior, inferolateral, or posterior; and 25 (39%) were subendocardial or non-Q wave infarcts. Sixteen patients (25%) had no complications observed during a hospital stay. The following complications were recorded among patients with an acute MI: ventricular arrhythmias or heart block, 34%; congestive heart failure, 31%; cardiogenic shock, 3%; and recurrent chest pain, 32%. A total of 23 persons (36%) were referred for further cardiac evaluation, such as an exercise stress test or coronary angiography. With regard to outcome, ten patients (16%) died within a month of the acute MI. Another 5 patients (8%) died before the date of chart review (July 1986), while 48 (75%) were presumed to be still alive.

Smoking, hypertension, and obesity were significantly more frequent among Sioux patients with acute MI than among a group of previously studied Navajo patients with the same disorder (Table 2).[14]

Sudden Deaths

In all, 43 sudden deaths were identified by death certificates using the specified ICD-9 codes. Eight patients were admitted to hospital, and four of these were ascertained on

TABLE 1.—*Age-Specific Annual Rates per 1,000 Persons of Confirmed Acute Myocardial Infarction: Sioux, Navajo, and Framingham Studies*

Age/Sex Groups, Years	Sioux, 1983-1985 (n=64)	Navajo, 1976-1979 (n=61)	Navajo, 1980-1983 (n=83)	Navajo, 1984-1986 (n=157)	Framingham*
Men					
35-44		0.1	0.1	0.4	2.1
45-54	4.2	0.7	0.5	1.7	5.4
55-64	10.0	0.9	1.3	2.6	9.1
65+	13.3	2.4	2.2	5.0	11.9†
35+	6.9	0.8	0.8	2.0	7.1
Women					
35-44		0.0	0.1	0.0	0.2
45-54	0.5	0.0	0.3	0.5	0.9
55-64	8.0	0.1	0.8	0.7	2.5
65+	16.2	0.6	1.8	2.3	5.1†
35+	4.0	0.1	0.5	0.6	2.2

*Framingham cohort based on 26-year follow-up (Kannel et al[13]).
†Data are listed as "65-74" years for Framingham group.

TABLE 2.—*Comparison of Risk Factors in Acute Myocardial Infarction Patients, Navajo and Sioux*

Risk Factors	Sioux, 1983-1985 (n=64), %	Navajo, 1976-1983 (n=144), %	χ^2, 1 df	P
Hypertension	53	36	10.22	.001
Smoke cigarettes	56	19	36.84	.001
Diabetes mellitus	40	32	1.48	NS
Obesity*	62	23	30.48	.001

*When both height and weight were noted on the chart, obesity was diagnosed if the person was more than 10% above the upper limits of normal weight for a large-framed person of the given height (Metropolitan Life Insurance Company[14]). In most cases, height was not recorded and the person was considered "obese" if such a diagnosis was recorded.

*International Classification of Diseases, 9th Revision—Clinical Modification. Ann Arbor, Mich, Commission of Professional and Hospital Activities, 1978

chart review to have died of other causes. Thus, there were 39 additional presumed cardiac-related sudden deaths of Sioux Indians in the four counties. Of these persons, 4 were admitted for care in non-IHS facilities, 4 were nursing home patients, and the other 31 died outside a medical facility. None had known noncardiac conditions that could be responsible for death. Of the sudden deaths, 13 (33%) occurred in women, as compared with 24 (37%) of the confirmed acute myocardial infarctions. The age distribution of the patients also corresponded with that observed for acute MI, further suggesting that these deaths were cardiovascular catastrophes. Only 15 deaths in patients with confirmed acute MI were observed during the three-year period. Thus, sudden death occurred between two and three times more frequently than death from hospital-diagnosed acute MI.

Discussion

Morbidity and mortality rates from cardiovascular disease and acute MI among Northern Plains Indians are higher than those among the United States population. This hospital chart study confirms the high attack rate of acute MI among Sioux Indians, particularly in comparison with that observed in the Navajo, an American Indian tribe with a different genetic and cultural background and, until recently, less exposure to contemporary life-styles. As only 68% of discharge diagnoses met our diagnostic criteria, acute MI may be somewhat overdiagnosed in these hospitals. Most of the other patients, however, did, in fact, have objective evidence of ischemic heart disease. The clear misclassification rate was only about 8%.

Hospital-diagnosed acute MIs constitute only one part of the total morbidity of acute myocardial infarction. From 25% to 40% of all acute MIs may be "silent," either entirely asymptomatic or producing atypical symptoms.[15,16] In addition, total ischemic heart disease mortality figures include "sudden deaths" that are presumed due to either acute MI or primary ventricular arrhythmias. Nearly two thirds of all deaths due to coronary artery disease in the United States are sudden deaths.[17] We found that there were 39 sudden deaths as compared with 15 acute MI deaths during this three-year interval. This almost 3:1 ratio of sudden to acute MI deaths in Sioux Indians suggests that a better use of hospital facilities and improved emergency transport services could prevent some of these deaths. The failure to reach a hospital could be caused by a reluctance to seek care, perhaps because of an inadequate recognition of cardiac symptoms, or by poor access due to a geographic remoteness or inadequate communications. Recent drunkenness has been associated with sudden deaths,[18] and the role of excessive alcohol intake in the high proportion of sudden deaths in Sioux should be evaluated further.

Low rates of ischemic heart disease among the Navajo are not entirely explained by known risk factors because, although few Navajos smoke cigarettes, diabetes mellitus and hypertension are prevalent.[19] Nonetheless, the Sioux and other Northern Plains Indians have high rates of diabetes, obesity, hypertension, and cigarette smoking,[20-24] which lead to potentially preventable morbidity and mortality from cardiovascular disease.[25] Recently the IHS has formulated goals with regard to such risk factors among the approximately 937,000 American Indians and Alaskan Natives for whom it provides health care.[1] For example, in 1987 the IHS announced a new policy to eliminate smoking by employees and patients in all of its health facilities.[22] Smoking cessation, blood pressure control, and weight reduction are important preventive measures that should be promoted in culturally acceptable ways among the Sioux. In addition, improvements in prehospital care may reduce mortality from sudden death.[13,26]

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Fetal Tissue Sampling
The San Francisco Experience With 190 Pregnancies

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Prenatal diagnosis of genetic defects was done using fetal blood sampling in 167 at-risk pregnancies, by fetal skin biopsy in 15 pregnancies, and by fetal liver biopsy in 8 pregnancies. Fetal blood sampling was done by fetoscopy through January 1985 and by sonographically directed percutaneous umbilical blood sampling since then. In our series, cytogenetics has become the major indication for fetal blood sampling, increasing from 6% of the cases with fetoscopy to 48% with umbilical blood sampling. Fetoscopy provided pure fetal blood in 61% of cases while umbilical blood sampling provided pure fetal blood 97% of the time. The corrected risk of fetal demise after percutaneous umbilical fetal blood sampling was 2% and after fetoscopy was 4%.

(Golbus MS, McGonigle KF, Goldberg JD, et al: Fetal tissue sampling—The San Francisco experience with 190 pregnancies. West J Med 1989 Apr; 150:423-430)

Advances in prenatal and neonatal care have lowered perinatal mortality rates so that genetic disorders represent a larger component of the residual mortality rate. Our ability to obtain information regarding the genetic status of a fetus has increased dramatically. Prenatal diagnostic techniques have made it possible, in many instances, to convert genetic counseling from an essentially passive endeavor to one in which parents can take steps to alter their reproductive genetic risks. The objective of prenatal diagnosis is to determine whether a fetus at risk for a particular genetic disease is or is not actually affected.

In utero sampling of fetal blood, skin, and liver has become an important tool in prenatal diagnosis and pregnancy management. As techniques have improved and experience has increased, the safety and efficacy of such sampling have improved dramatically. As the fetal risk with fetal tissue sampling has decreased, indications have broadened. Concurrently, as DNA techniques for prenatal diagnoses have developed, there has been a reduced requirement for in utero tissue sampling for many of these particular disorders. In this report we summarize ten years of experience with in utero tissue sampling at the University of California, San Francisco (UCSF).

Patients and Methods

At-risk patients were referred to the Reproductive Genetics unit of UCSF between June 1977 and December 1987 for various prenatal diagnoses or for pregnancy management. Diagnostic fetal blood sampling was done in 167 pregnancies using fetoscopy (90 cases) or percutaneous umbilical blood sampling (PUBS) (77 cases). Fetal blood sampling was done by fetoscopy or percutaneously from umbilical cord blood between 18 and 37 menstrual weeks. Fetal skin biopsies were done in 15 pregnancies and fetal liver biopsies in 8 pregnancies using sonographic guidance and fetoscopy. Fetal skin or liver biopsies were done between 18 and 23.5 menstrual weeks. All patients gave informed consent as per a protocol approved by the University of California Committee on Human Research.

Fetoscopy was done between June 1977 and January 1985 using the 2.2- by 2.7-mm Dyonics fetoscope, which allowed passage of the scope and sampling needle through one trocar. Using a 26- or 27-gauge needle, the fetal umbilical cord or placental surface vessels were punctured under direct vision with the fetoscope. For PUBS a 22- or 25-gauge spinal needle was used to puncture the cord directly under ultrasonic guidance. If the placenta was anterior, it was entered and the cord punctured without entering the amniotic cavity. If the placenta was posterior, the amniotic cavity was entered and the cord punctured 1 to 2 cm from its insertion into the placenta. Using either fetoscopy or PUBS, up to 2 ml of fetal blood was withdrawn depending on the gestational age and quantity required for the specific analysis. Fetal blood was aspirated into either heparinized syringes or, in cases where hemophilia was the indication, into syringes containing 3.8% sodium citrate solution. The presence of fetal blood was immediately confirmed using a model ZBI Coulter counter and channelizer that differentiates fetal from maternal blood on the basis of erythrocyte volume. Early in the experience, smears from the specimen were subsequently stained by the Betke-Kleihauer method to verify the presence of fetal cells.

Fetal liver biopsies were done under sonographic guidance using a disposable 16.5-gauge thin-wall Lee biopsy needle (Becton-Dickinson, Rutherford, NJ). A single entry into the fetal liver was made immediately below the right costal margin. A 3-ml syringe was attached to the needle and negative pressure applied to bring liver tissue into the biopsy needle. The tissue was flushed from the needle with ice cold 0.9% saline solution into 1.5-ml conical microtubes and immediately centrifuged to differentiate liver tissue from blood

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ABBREVIATIONS USED IN TEXT

PUBS = percutaneous umbilical [cord] blood sampling
UCSF = University of California, San Francisco

contamination. Further specimens were obtained to provide sufficient tissue as needed. The method for liver biopsy and ornithine transcarbamylase analysis and glucose-6-phosphatase analysis has been described from this institution.[1,2]

Initially fetal skin biopsies were done using fetoscopy. Using ultrasound guidance, the Dyonics fetoscope was used to clearly visualize the fetal skin and was placed firmly on the appropriate fetal part and the trocar withdrawn. A cupped biopsy forceps (20 cm) was passed down the cannula, and skin specimens (2 mm) were obtained. More recently skin biopsies have been done entirely under ultrasound guidance without direct visualization. After sampling, the tissue was immediately placed in minimal essential medium with 20% fetal calf serum. Within minutes the tissue was transferred to cacodylate-buffered 1.5% glutaraldehyde solution and then postfixed in osmium tetroxide; tissue 1 μm thick was embedded in Araldite 506 for electron microscopy and light microscopy. The methods to evaluate fetal skin for various prenatal diagnoses have been well described.[3-13]

Before any sampling procedure, the patient was usually premedicated with intravenous diazepam (Valium), and a local anesthetic was injected intradermally and subdermally. Patients were usually given prophylactic intra-amniotic antibiotics after liver or skin biopsy but not after blood sampling. In Rh-negative patients, fetal blood typing was done, and, if indicated, the patient was given Rh_0(D) immune globulin, the amount depending on the results of a maternal Betke-Kleihauer test done an hour after the procedure. The patient and fetus were observed for four to six hours and then discharged.

Results

Fetal Blood Sampling

A total of 167 pregnancies underwent fetal blood sampling either using fetoscopy from June 1977 through January 1985 or percutaneous umbilical blood sampling from February 1985 through December 1987. A total of 94 fetal blood samplings were done in 90 pregnancies in 83 patients using fetoscopy. Five patients had fetoscopy done in consecutive pregnancies, two in three pregnancies and three in two pregnancies. Two other patients had fetoscopy and then PUBS done in two pregnancies. Fetoscopies were repeated in four pregnancies. Using PUBS, a total of 96 fetal blood specimens were taken in 77 pregnancies in 76 patients. Excluding patients with erythrocyte isoimmunization who have multiple fetal blood samplings done before serial intrauterine transfusions and one patient with alloimmune thrombocytopenia who underwent serial fetal platelet measurements, only one patient had repeat fetal blood sampling by PUBS. Percutaneous umbilical blood sampling for erythrocyte isoimmunization was done 26 times in 10 pregnancies.

Indications for fetal blood sampling by fetoscopy (June 1977 through January 1985) and PUBS (February 1985 through December 1987) are listed in Table 1. The most common indication before February 1985 was the risk of a hemoglobinopathy (52%), and the risk of coagulopathies was the second most common (27%). After February 1985 the most common indication became cytogenetic (48%), with hemoglobinopathies second (16%), erythrocyte isoimmunization third (13%), and coagulopathies fourth (12%) (Figures 1 and 2).

The median duration required to do fetal blood sampling in all patients using fetoscopy where a specimen was obtained was 23.5 minutes and in patients in whom hemophilia was the indication (and mixed specimens were not adequate) was 31 minutes. Excluding hemophilias, the median duration was 22 minutes. This difference was not statistically significant. Using PUBS the median procedure time was six minutes for all patients and five minutes for patients in whom hemophilia was the indication.

Fetoscopy. Patients undergoing fetoscopy were followed up to delivery in 94% of cases (85 of 90 pregnancies). In all, 25 patients had a therapeutic pregnancy termination because of a positive prenatal diagnosis (28%). In the 53 patients whose pregnancies were carried and for whom there is follow-up, 9 (17%) were delivered preterm. In one of these, a cesarean section was done at 36 weeks for placenta previa, and in another the fetus was delivered at 32 weeks because of nonimmune hydrops. In the other seven patients there is no clear cause for the preterm delivery, only one of which occurred before 34 weeks. The corrected preterm delivery rate is 7 of 51 (14%). Fetal demise after fetoscopy for fetal blood sampling occurred in seven cases. Two of the seven occurred after intracardiac sampling following unsuccessful fetal blood sampling by fetoscopy for hemophilia A of normal fetuses. A third occurred three days after sampling of a fetus

TABLE 1.—*Indications for Fetal Blood Sampling*

Indication	Fetoscopy (n=90), No. Pregnancies	(%)	Percutaneous Umbilical Blood Sampling (n=77), No. Pregnancies	(%)
Cytogenetics	5	(6)*	37	(48)
Hemoglobinopathies	47	(52)	12	(16)
β-Thalassemia	28		4	
α-Thalassemia	3		2	
Sickle cell anemia	9		4	
Compound heterozygotes	7		2	
Sickle-β-thalassemia	4		2	
Sickle cell disease	2		0	
Hemoglobin E-β-thalassemia	1		0	
Erythrocyte isoimmunization	0		10	(13)
Coagulopathies	24	(27)	9	(12)
Hemophilia A	24		4	
Hemophilia B	0		5	
Immunologic	7	(8)	5	(6)
Severe combined immunodeficiency	1		5	
Chédiak-Higashi syndrome	1		0	
Chronic granulomatous disease	3		0	
Wiskott-Aldrich syndrome	2		0	
Miscellaneous	7	(8)	4	(5)
Duchenne muscular dystrophy	3		0	
Paternity	1		0	
Abetalipoproteinemia	1		0	
α_1-Antitrypsin	1		0	
Nonimmune hydrops	1		2	
Rubella infection	0		1	
Alloimmune thrombocytopenia	0		1	

*Percentages exceed 100 because of rounding.

affected with hemophilia A. Three others occurred in or before 1978 when fetoscopy experience was minimal.

Sampling problems with fetoscopy for fetal blood sampling. In 55 of 90 pregnancies (61%), pure fetal blood specimens were obtained using fetoscopy. Pure fetal blood is required for a diagnosis of hemophilia, whereas for some other disorders a mixed specimen is acceptable for analysis. A successful specimen was obtained on the first attempt in 72 of 90 (80%) pregnancies using fetoscopy. Eventually, a specimen adequate for prenatal diagnosis was obtained in 81/90 pregnancies (90%). In four pregnancies, the fetoscopy was repeated; in one of these, a pure fetal blood specimen was not obtained with repeat fetoscopy but was obtained after intracardiac sampling. In eight pregnancies, placentesis[14] was attempted immediately after the failure to obtain an adequate specimen with fetoscopy. In six of those eight, an adequate specimen was obtained. In six patients with fetuses at risk for hemophilia A, the initial sampling was inadequate. In three of these patients, blood was obtained by intracardiac sampling, which was associated with fetal death in two. In one patient who underwent fetal blood sampling for cytogenetics to confirm a twin with 46,XY,9p− before selective termination, although a pure fetal blood specimen was obtained, it was diluted with amniotic fluid and no metaphases were found.

Percutaneous Umbilical Blood Sampling

A follow-up to delivery was done in all pregnant patients undergoing fetal blood sampling by the percutaneous umbilical method. A total of 14 pregnancies were electively terminated. Of 57 pregnancies that were carried, 22 (39%) were delivered preterm. Amnionitis developed in one patient at 28 menstrual weeks after PUBS for severe combined immunodeficiency, and she was delivered of an unaffected fetus three days after the PUBS. In 17 patients, preterm delivery was related to the high-risk nature of the pregnancy. The other four were delivered preterm without an obvious cause.

Fetal demise occurred in six pregnancies. One fetus died after its acephalocardiac monozygotic twin was removed. Another fetus died during an in utero operation for correction of a congenital diaphragmatic hernia. A third fetus with trisomy 18 died a few days after PUBS for karyotyping. The fourth demise was after a PUBS procedure in a fetus affected with hemophilia A. The fifth demise occurred in a 20.5-week hydropic fetus during an attempted intrauterine transfusion one day after a PUBS showed a hematocrit of 0.12 due to a fetomaternal hemorrhage. In the sixth case, the fetus died a few days after a fetal blood sampling for trisomy 21 amniotic fluid mosaicism. The karyotype of the fetal blood was normal. This was the only pregnancy undergoing a PUBS where an apparently normal fetus died.

Sampling problems with PUBS. Sampling problems were minimal using PUBS, and pure fetal blood specimens were obtained in 97% of the cases. A specimen was successfully obtained on the first attempt in all but one pregnancy. In this pregnancy, a specimen of 100% fetal blood was obtained at PUBS for severe combined immunodeficiency, but another specimen was needed to adequately study the lymphocytes because of a laboratory error.

Indications

Cytogenetics

Karyotyping of phytohemagglutinin-stimulated fetal peripheral blood lymphocytes was a common indication for fetal blood sampling. A major advantage of blood sampling over amniocentesis was that results were available in 48 to 72 hours. Thus, blood sampling was often done in cases where rapid decisions on fetal intervention needed to be made. One common indication was to rule out a chromosomal abnormality in a structurally abnormal fetus either before a fetal

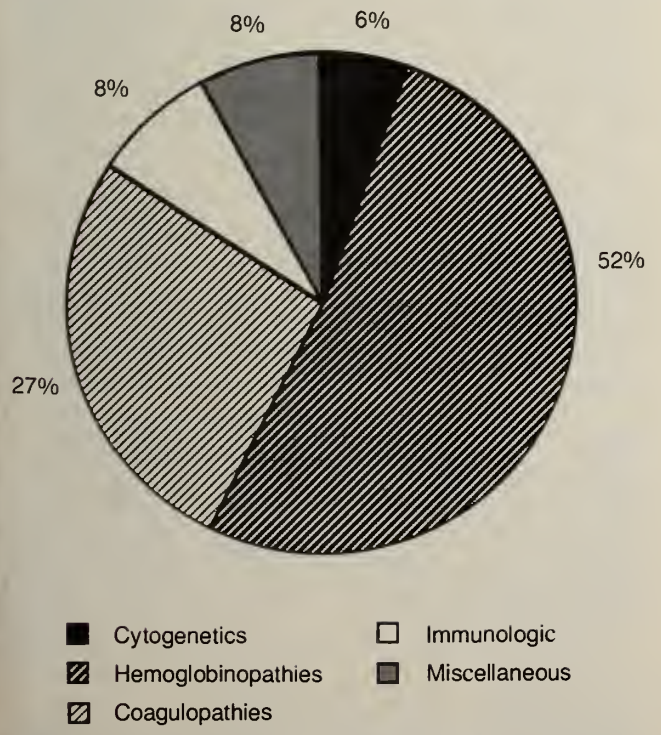

Figure 1.—The proportion of pregnancies having fetal blood sampling by fetoscopy is shown for various indications.

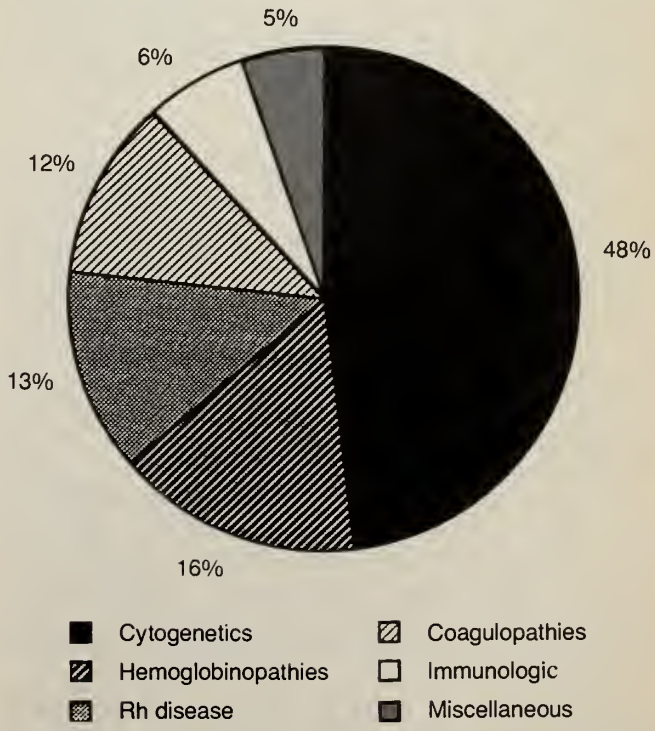

Figure 2.—The proportion of pregnancies having fetal blood sampling by percutaneous umbilical blood sampling is shown for various indications.

operation or to aid in the management of the pregnancy, delivery, and neonate. Other indications included clarification of chromosome mosaicism after a previous prenatal diagnosis by amniocentesis or chorionic villus sampling or to verify a chromosomal abnormality of a twin before a selective termination (Table 2). Karyotyping was also commonly done on fetal blood taken not primarily for a chromosome study but for other indications. This was done in almost all cases in which a previous karyotype had not been determined by chorionic villus sampling or amniocentesis. In all such cases the chromosomes were normal.

Hemoglobinopathies

Fetal blood sampling was done for 59 women at risk of carrying a fetus with a hemoglobinopathy. Many of these conditions now can be diagnosed by DNA analysis,[15-18] but analyzing a blood specimen may be more rapid and is still done for at-risk couples presenting late in the second trimester. Thalassemia diagnoses using fetal blood were made by examining globin-chain-synthesis ratios.[19-21] If pure fetal blood was obtained, isoelectric focusing was done to confirm the globin-chain analysis. If not, confirmatory isoelectric focusing was done on cord blood after delivery. In those fetuses affected with the abnormal homozygous state, termination was generally requested and carried out. Although we attempted to verify the diagnosis in each case, this was not always possible as some patients chose to have a termination procedure in which blood might not have been obtainable at delivery of the fetus. There were no misdiagnoses among validated specimens. The results of fetal blood sampling for this indication are listed in Table 3.

Isoimmunization

Fetal blood sampling was done for ten patients with erythrocyte isoimmunization either to test the fetal blood type to avoid serial amniocenteses of an Rh-negative fetus (two cases) or to determine the fetal hematocrit before an intrauterine fetal blood transfusion (eight cases). All blood sampling was by PUBS with a total of 26 sampling procedures.

Coagulopathies

Fetal blood sampling was done for 33 patients at risk of carrying a son with hemophilia A or B. A valid method of evaluating for hemophilia A using fetal blood was developed in 1978[22] using factor VIII coagulant antigen (VIII:CAg) and factor VIII-related antigen (VIIIR:Ag) values. For hemophilia A, the specimen must be greater than 90% fetal blood and the fetal blood must be at least 10% of a blood and amniotic fluid mixture, or the specimen cannot be adequately evaluated. For hemophilia B, a similar assay is used for diagnosis,[23] but the specimen must be 100% fetal blood without amniotic fluid dilution. In the past few years many cases of hemophilia A and B also could be diagnosed by DNA analysis of chorionic villi or amniocytes[24,25] so that the need to do blood sampling for these patients has dropped dramatically.

In all affected cases, pregnancies were terminated. An attempt to confirm the results after termination was made in each case but was not always possible because of an inability to obtain fetal blood at the time of pregnancy termination. There were no misdiagnoses among cases when blood was obtained. Results of fetal blood sampling for hemophilia A from 1979 through 1984 have been previously reported.[22] The results of sampling for hemophilias are listed in Table 4.

Immunologic

Fetal blood sampling was done for 12 patients at risk of carrying a fetus with autosomal or sex-linked recessive immunologic deficiencies. Sampling was done for this indication for severe combined immunodeficiency, the Chédiak-Higashi syndrome, the Wiskott-Aldrich syndrome, and chronic granulomatous disease. Methods to evaluate fetal blood for severe combined immunodeficiency have been well described,[26-28] as have those for the other diagnoses.[29-31] In one case in a fetus at risk for immunodeficiency, immunologic studies of fetal blood revealed normal T cells and a

TABLE 2.—*Fetal Blood Sampling for Cytogenetic Indications*

Indication	*Fetoscopy (n=5), Number*	*Percutaneous Umbilical Blood Sampling (n=37), Number*	*Total (n=42), No. (%)*
Structural anomalies	0	16	16 (38)
Normal results		14	
Abnormal results		2	
Mosaicism on CVS or amniocentesis	2	13	15 (36)
Normal results	2	9	
Abnormal results	0	3	
No results		1	
Twin gestation for selective termination	2	7	9 (21)
Nonimmune hydrops	1	1	2 (5)
Normal results	1	1	

CVS = chorionic villus sampling

TABLE 3.—*Fetal Blood Sampling for Hemoglobinopathies*

Hemoglobinopathy	*Fetoscopy (n=47), Number*	*Percutaneous Umbilical Blood Sampling (n=12), Number*	*Total (n=59), No. (%)*
β-Thalassemia	28	4	32 (54)
Unaffected	21	3	24
Affected	6	1	7
No results	1	0	1
Sickle cell anemia	9	4	13 (22)
Unaffected	5	4	9
Affected	4	0	4
Compound heterozygotes	7	2	9 (15)
Unaffected	5	2	7
Affected	2	0	2
α-Thalassemia	3	2	5 (8)
Unaffected	2	1	3
Affected	1	1	2

TABLE 4.—*Fetal Blood Sampling for Hemophilia*

Hemophilia	*Fetoscopy (n=24), Number*	*Percutaneous Umbilical Blood Sampling (n=9), Number*	*Total (n=33), No. (%)*
Hemophilia A	24	4	28 (85)
Normal	11	3	14
Affected	10	1	11
No results	3	0	3
Hemophilia B	0	5	5 (15)
Normal		3	3
Affected		2	2

slightly decreased number of B cells consistent with an unaffected fetus. At delivery, however, the fetus was affected. In all other cases, the results after delivery or termination were consistent with the prenatal diagnosis. The results of fetal blood sampling for immunologic indications are given in Table 5.

Miscellaneous

Miscellaneous indications for fetal blood sampling are listed in Table 1. Seven such patients underwent sampling by fetoscopy and four by PUBS. These miscellaneous indications included Duchenne's muscular dystrophy,[32] α_1-antitrypsin deficiency, abetalipoproteinemia,[33] paternity identification,[34] nonimmune hydrops, fetal infection, and alloimmune thrombocytopenia.

Fetal Skin Sampling

Fetal skin sampling was carried out for prenatal diagnosis in 15 pregnancies in 11 patients between January 1979 and December 1987. Four patients had sampling done in two separate pregnancies. Indications included harlequin ichthyosis, epidermolysis bullosa, and autosomal-dominant ichthyosiform erythroderma (Table 6).

Follow-up to delivery was obtained in 14 of 15 delivered patients. Of these 14 patients, 2 were delivered preterm. Another patient had a spontaneous abortion associated with chorioamnionitis two days after the sampling procedure. A satisfactory skin specimen was obtained in 14 of 15 pregnancies. The median amount of time to do the sampling in these 14 patients was 13 minutes. In the two patients who were delivered preterm and the one where a fetal demise occurred, the median procedure time was 38 minutes.

Following delivery, a skin biopsy was generally not necessary to confirm a normal diagnosis. After a therapeutic or spontaneous abortion, however, the results of the prenatal sampling were confirmed by autopsy. In one case where sampling was done for ichthyosiform erythroderma, although the results of the sampling were normal, the infant was found to be mildly affected after delivery. In all other cases, the prenatal diagnosis was confirmed after delivery or termination.

Fetal Liver Sampling

A fetal liver biopsy was done in eight pregnancies in six patients between June 1982 and May 1986. Two patients had fetal liver biopsies done in two separate pregnancies. In two patients, sampling was attempted three times in the same pregnancy, and a satisfactory specimen was obtained in one. In the second, no specimen was ever obtained. Indications for fetal liver sampling are shown in Table 7.

Patient follow-up to delivery was obtained in all eight pregnancies. Four were carried uncomplicated to term. There were no preterm deliveries or spontaneous abortions. The other four had therapeutic abortions of affected fetuses. After termination, the prenatal diagnosis was confirmed. After birth, infants were tested if indicated clinically. There were no misdiagnoses.

Discussion

Fetal tissue sampling has become a relatively common diagnostic tool. This study shows that new technology and experience have allowed it to become a safer, simpler technique with excellent results in nearly all cases.

Fetal Blood Sampling

The present study evaluates the experience with fetal blood sampling at the University of California, San Francisco, since 1977. Before June 1977, placentesis was used to sample fetal blood.[14] This technique commonly provided mixed fetal and maternal blood specimens[35-37] and was satisfactory for the diagnosis of most hemoglobinopathies. Fetoscopy improved fetal blood sampling so that 100% fetal blood was obtained more frequently (in 61% of specimens in this study), allowing indications to broaden to include hemophilia A and various immunologic diseases where pure or nearly pure fetal blood was required. Using fetoscopy, how-

TABLE 5.—*Fetal Blood Sampling for Immunologic Indications*

Indication	*Fetoscopy (n=7), Number*	*Percutaneous Umbilical Blood Sampling (n=5), Number*	*Total (n=12), No. (%)*
Severe combined immunodeficiency	*1*	*5*	*6 (50)*
Normal	0	5	5
Affected	0	0	0
No results	1	0	1
Chronic granulomatous disease	*3*	*0*	*3 (25)*
Normal	3		
Wiskott-Aldrich syndrome	*2*	*0*	*2 (17)*
Normal	1		
No results	1		
Chédiak-Higashi syndrome	*1*	*0*	*1 (8)*
Normal	1		

TABLE 6.—*Fetal Skin Sampling Indications*

Indication	*Pregnancies Evaluated (n=15), Number*
Epidermolysis bullosa	*8*
Normal	8
Harlequin ichthyosis	*5*
Normal	3
Affected	1
No results	1
Ichthyosiform erythroderma	*2*
Normal	1*
Affected	1

*The results of fetal skin sampling were normal; after delivery, the infant was found to be mildly affected.

TABLE 7.—*Fetal Liver Sampling Indications*

Indication	*Pregnancies Evaluated (n=8), Number*
Ornithine carbamylase deficiency	*4*
Normal	0
Affected	3
No results*	1
Glycogen storage disease type IA	*3*
Normal	2
Affected	1
Nonketotic hyperglycemia	*1*
No results*	1

*Normal at delivery.

ever, fetal blood was often contaminated with amniotic fluid. Additionally, fetoscopy could not be used if the amniotic fluid was discolored and was less efficacious later in pregnancy because the fluid is then less clear. Similarly, fetoscopy could not be immediately repeated if an adequate specimen was not obtained as maternal blood usually contaminated the amniotic fluid. With the dramatic improvements in ultrasonographic technology, percutaneous umbilical blood sampling has replaced fetoscopy because of its safety, simplicity, and ability to obtain 100% fetal blood without amniotic fluid contamination in nearly all cases.

The timely division of the fetoscopy era (June 1977 to January 1985) versus the PUBS era (February 1985 to December 1987) provides a simple means of showing the changing indications for fetal blood sampling at UCSF (Figures 1 and 2). This is exemplified in the present study where hemoglobinopathies were the indication in 52% of pregnancies evaluated during the fetoscopy era and in only 16% during the PUBS era. Similarly, coagulopathies were the indication for fetal blood sampling with fetoscopy in 27% of pregnancies, whereas with PUBS, coagulopathies were the indication in only 12%. In recent years, DNA techniques have been developed for the diagnosis of both hemophilia A and hemophilia B.[24,25] Similarly, DNA techniques now exist for most hemoglobinopathies[15-18] and for α_1-antitrypsin deficiency,[38] reducing the need for fetal blood sampling for these indications.

Cytogenetic evaluation has become the major indication for fetal blood sampling, increasing dramatically from 6% of the cases with fetoscopy to 48% with PUBS. Probable reasons for this include the following:

- The widespread use of amniocentesis and chorionic villus sampling for karyotyping has increased the need for fetal blood sampling to rule out mosaicism;
- As techniques for selective termination have developed, so has the need to do fetal blood sampling for rapid karyotyping to confirm which is an abnormal twin;
- As the risk of blood sampling has decreased dramatically, sampling for karyotyping a structurally abnormal or hydropic fetus has become more common; and
- There has developed an increased awareness of the high association of chromosomal abnormalities with various fetal anomalies.[39]

Fetal blood sampling was not done at UCSF during the fetoscopy era for erythrocyte isoimmunization. A recent study by Nicholaides and co-workers comparing results of fetal blood sampling with amniotic fluid spectrophotometric readings of net absorbance at 450 nm showed that although there was a significant correlation between fetal anemia and these readings, the results were too widely scattered to predict the severity of anemia in second-trimester fetuses.[40] Thus, it appears that blood sampling for fetal hematocrit allows a more appropriate management of pregnancies in which amniotic fluid studies predict fetal anemia in the second trimester. Additionally, with the use at our institution of intravascular intrauterine transfusions for severe isoimmunization, either in addition to or in place of intraperitoneal transfusions, fetal blood sampling has become part of the standard management of these patients.

Although prenatal infection was the indication for fetal blood sampling in only one pregnancy in this study, other institutions have reported that evaluating for congenital cytomegalovirus infection and for rubella infection was common for fetal blood sampling.[41-43] This is likely related to geographic differences in the incidence and severity of these diseases.

In the future, fetal blood sampling for the evaluation of fetal acid-base status either before or during labor will likely become more common and already has been reported as an indication for PUBS at other institutions.[44-46] In addition, blood sampling has been used to measure fetal levels of digoxin in fetuses treated for supraventricular tachycardia.[42,47] Other possible uses include the measurement of glucose or insulin levels in the fetus of a diabetic mother and the evaluation of fetal growth retardation or of nonimmune fetal hydrops to better understand and treat these conditions. These indications may become more common as risks continue to decrease.

Fetoscopy provided pure fetal blood in 61% of cases, a higher percentage of cases than for placentesis.[14] A significant proportion of these specimens were contaminated with amniotic fluid. Percutaneous umbilical blood sampling nearly always—in 97% of cases in this study—provided 100% fetal blood without amniotic fluid contamination. Using fetoscopy, a specimen was successfully obtained in 80% of cases with the first attempt, and in 90% of cases a specimen was obtained after either repeat sampling with fetoscopy or using placentesis or intracardiac sampling. The development of PUBS virtually eliminated sampling problems so that a specimen was successfully obtained in essentially every case with the first attempt. Similarly, the median procedure time to obtain a specimen dropped dramatically. For fetoscopy it was 23.5 minutes and for PUBS 6 minutes, thus showing the greater simplicity of PUBS and the reduced fetal risk by a decreased procedure time.

Using fetoscopy, fetal demise occurred in seven cases, an uncorrected rate of 12% of continuing pregnancies. This is higher than the rates reported by others: 4.3%[48] and 6.8%.[49] The higher demise rate in our series is likely related to the following:

- Two cases were included wherein demise occurred after intracardiac sampling for hemophilia A, a technique that carries a far greater risk than fetoscopy and is usually fatal in an affected fetus. In most cases, coagulation factors from the mother in the amniotic fluid provide protection from fatal hemorrhage to the hemophiliac fetus after fetal blood sampling, and this protective factor is lost with intracardiac sampling.
- One of the fetuses was affected with hemophilia, which carries a higher risk of demise than for fetuses without a bleeding disorder.
- Three of the deaths occurred in 1978 or earlier when our experience with fetoscopy was limited.

Since 1980, 4 demises occurred in 47 continuing pregnancies (8%) undergoing fetoscopy. Excluding the two cases where demise occurred after intracardiac sampling, there were only 2 demises in 45 pregnancies, or 4%.

Using PUBS, fetal loss occurred in six pregnancies, for an uncorrected rate of 10% of continuing pregnancies. This is higher than the 1.9% reported by Daffos and associates[41] and is likely related to the high-risk population in this study. In only one case did a demise occur in an unaffected fetus. Thus, the corrected risk of fetal demise after fetal blood sampling was closer to 1 in 58 (2%). Of particular interest is

the demise that occurred in a 20.5-week hydropic anemic fetus with a hematocrit of 0.12 due to a fetomaternal bleed. Bradycardia occurred and the fetus died during an attempted intrauterine transfusion. A similar observation was made by Benacerraf and colleagues in a 31-week fetus with severe anemia due to a fetomaternal bleed[50]; in their case, however, because of the viable gestational age, an emergency delivery averted an in utero demise. They postulated that the low hematocrit of the fetus predisposed the cord to venospasm. Theoretically, this would increase the risk of fetal blood sampling in severely anemic fetuses. Interestingly, this problem was not observed in 26 fetal blood samplings of isoimmunized fetuses, many of whom were severely anemic before an intrauterine transfusion. Perhaps it is related to the fact that the erythrocyte isoimmunization anemia arises slowly while the anemia of fetomaternal hemorrhage occurs abruptly.

Preterm delivery occurred in nine (17%) continuing pregnancies using fetoscopy. This is higher than that reported by some—6%[19]—and similar to that reported by others—15%.[36] In the present study, two of these patients carried independent risk factors for early delivery: placenta previa and nonimmune hydrops. In six of these patients, delivery occurred at or later than 34 weeks. It is unclear why such a high proportion of the preterm deliveries were relatively late. Because of this fact, the morbidity was minimal and none of the infants required artificial ventilation for respiratory distress. Ward and co-workers also noted a high incidence of "late" preterm deliveries in fetoscopy patients: more than 50% of their preterm cases occurred at 35 and 36 weeks.[36] Using PUBS, the preterm delivery rate was 39% (22 of 57 continuing pregnancies). This is much higher than the 5% reported by Daffos and associates[41] and is likely related to the high-risk population sampled. In 32 of 77 (42%) of the pregnancies in which PUBS was done, the risk of preterm delivery is known to be much higher than in the general population. These include fetuses with structural anomalies, nonimmune hydrops, erythrocyte isoimmunization, alloimmune thrombocytopenia, fetuses who underwent an in utero operation, and twins for selective termination. Of 22 preterm deliveries, 17 occurred in such high-risk pregnancies; the corrected preterm delivery rate was 12% (5 of 40).

In nearly all cases where studied, the prenatal diagnosis was confirmed after delivery or termination. In only one case was an incorrect diagnosis made in a fetus at risk for severe combined immunodeficiency.

Fetal Skin Sampling

Fetal skin sampling is the only method available to prenatally diagnose many of the severe and often fatal genodermatoses. Sampling was done in 15 patients. Because of the small number, it is impossible to evaluate the rates of demise and preterm delivery. In one case where a skin specimen was taken for autosomal-dominant ichthyosiform erythroderma, an incorrect diagnosis was made. Improved techniques have theoretically made fetal skin sampling a safer procedure by allowing more rapid sampling.

Fetal Liver Sampling

Fetal liver sampling was carried out in eight pregnancies. This is the largest reported group of pregnancies undergoing fetal liver sampling. Half of the pregnancies were affected, and pregnancy termination was chosen by the couples. There were no demises or preterm deliveries in the remaining four. There were no misdiagnoses. Recently a DNA technique for the prenatal diagnosis of ornithine transcarbamylase deficiency has been developed that will decrease the need for fetal liver sampling for this indication.[51]

Conclusion

The experience with fetal tissue sampling at UCSF confirms that it is efficacious and has broad clinical applications that are changing yearly. It has become a much safer technique over the years with risks approaching, but still greater than, those seen with amniocentesis and chorionic villus sampling. Thus, these more sophisticated techniques should be used judiciously. It is likely that they will continue to be useful tools with even more applications in the future.

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Fish Oil Capsules

WITH ALL THE RECENT PUBLICITY, many people ran out and bought fish oil capsules. People were taking 600 to 700 extra calories a day in fish oil capsules! Ads in medical journals told us that there was a decrease in coronaries because of fish oil intake. No such data exist. The Eskimo has a high fat diet, a 26% protein diet, and, in fact, the only thing fish oil does is decrease triglyceride concentrations. The VLDL particle goes down. Fish oil can be a fantastic therapy for type IV, type V (hyperlipidemias); it does very little for type II.

—WAYNE R. BIDLACK, PhD

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Medical Progress

Diagnosing and Treating Active Myocarditis

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The treatment of dilated cardiomyopathy is palliative and, hence, has little effect on the natural history. Therapy directed toward the cause rather than the effect will be necessary before mortality can be affected. Active myocarditis is postulated to be the cause of dilated cardiomyopathy in a subset of patients. A model of murine coxsackievirus B3 myocarditis has immunopathogenic parallels to the disease in humans and suggests that persistent autoimmune reactivity following viral clearance leads to progressive myocyte damage and dilated cardiomyopathy. In preliminary uncontrolled studies, patients with myocarditis have shown clinical and histologic improvement with the addition of immunosuppressive therapy, but there may also be a significant rate of spontaneous improvement. A multicenter study currently acquiring patients is designed to determine the efficacy of immunosuppression and the natural history of active myocarditis.

(O'Connell JB, Mason JW: Diagnosing and treating active myocarditis. West J Med 1989 Apr; 150:431-435)

Dilated cardiomyopathy is an important cause of congestive heart failure, affecting a young population and resulting in death in 50% within two years of diagnosis.[1] The treatment is palliative, designed primarily to alter the deleterious peripheral vascular compensatory mechanisms resulting from organ underperfusion.[2] Because there is no definitive treatment, this disorder remains the most common indication for cardiac transplantation.[3] Dilated cardiomyopathy includes a heterogeneous group of disorders in which myocarditis may be an important etiologic factor. Successful treatment of myocarditis when instituted early in the course of the disease might prevent irreversible myocardial damage.

Myocarditis May Be a Precursor of Dilated Cardiomyopathy

It has been more than 150 years since it was first postulated that an infectious agent *(Corynebacterium diphtheriae)* may elicit an inflammatory response that culminates in chronic myocardial disease.[4] Nevertheless, the ability to establish an accurate diagnosis of myocarditis during life has only recently become possible. Evidence supporting the concept that a viral infection leads to adverse immunologic responses culminating in dilated cardiomyopathy is largely circumstantial in human subjects (Table 1). An animal model has been developed that may shed some light on the human disease.

When coxsackievirus B3, the most commonly proposed etiologic vector of human myocarditis, or encephalomyocarditis virus is injected into selected murine strains, a self-limited infection of the myocardium results.[5] The infective phase is characterized by myocyte viral replication that is halted within seven to ten days after inoculation by interferon, macrophages, natural killer cells, and humoral antibody. During this acute phase, minimal myocyte necrosis is present with sparse inflammatory infiltration. As the virus is eliminated, lymphomononuclear cell infiltration intensifies. Chronic myocardial damage is inflicted by autodirected T lymphocytes in BALB/c and CD1 murine strains and by humoral antibody in DBA/J strains.[6] In the former, the stimulus may be either a fibroblast neoantigen[7] or cross-reactivity between myocyte and viral antigens.[8] In the DBA/J strain where humoral immune responses play a significant role, myosin is thought to be of antigenic importance.[9]

In outbred murine strains infected with coxsackievirus B3, dystrophic mineralization, myocyte hypertrophy, and interstitial fibrosis develop by six months in the presence of active inflammation.[10] By one year following infection, chamber dilatation and mural thrombi occur with histologic features similar to those in human cases of dilated cardiomyopathy.[11] In this advanced stage, inflammation is no longer present. During the early phase of the illness, the animal remains free of signs of congestive heart failure; by the end-stage ascites, peripheral edema and a loss of muscle mass occur as manifestations of chronic congestive heart failure. In summary, in the animal model, viral infection results in autoimmune responses after viral clearance that lead to progressive myocyte destruction, congestive heart failure, and death of the host.

It is easy and perhaps correct to postulate a similar pathogenesis in humans. Despite the large number of patients who have been thoroughly evaluated, including culture of myocardial biopsy specimens, only one adult has been reported to have active myocardial viral infection proved during life.[12] Until recently, the only feasible approach has been to infer active viral infection or a previous exposure to cardiotropic viruses by measuring neutralizing antibody titers. Fletcher and co-workers found a titer greater than 1:40 against coxsackievirus B in 30% of patients with dilated cardiomyopathy and 30% of controls.[13] Cambridge and associates, however, found a titer greater than 1:1,024 in 30% of patients with dilated cardiomyopathy and in only 2% of controls, suggesting that patients with the disorder had had expo-

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sure to cardiotropic viruses more frequently.[14] Eggers and Mertens measured neutralizing antibody titer against five coxsackievirus B serotypes in a normal population and found that by age 60 years, 53% had an elevated titer against at least one serotype, suggesting that exposure to cardiotropic viruses is common and an isolated measure of antibody titer may be meaningless.[15] Recombinant DNA technology and in situ hybridization are recently developed, highly sensitive techniques for detecting viral genomes. Bowles and colleagues developed a coxsackievirus B-specific complementary DNA hybridization probe to identify nucleic acid sequences in endomyocardial biopsy specimens.[16] Of 17 patients with "active" or "healing" myocarditis or "dilated cardiomyopathy with inflammation," 9 had positive hybridization signals, and of 4 biopsy specimens from patients with dilated cardiomyopathy without inflammation, none were positive. Verifying the specificity of the probes is of utmost importance. If sequences of the hybridization probe share similarities to human DNA or RNA sequences, false-positive signals may result. Nonetheless, these data, if confirmed, support the hypothesis that a viral infection leads to myocarditis and ultimately dilated cardiomyopathy.

Follow-up evaluation of patients with oropharyngeal cultures positive for coxsackievirus B was reported by Orinius[17]: 60 patients younger than 35 years had positive cultures in the absence of clinical evidence of myocarditis. Of these, 53 were evaluated six years after the positive culture was obtained and 10 (19%) had cardiac symptoms or electrocardiographic abnormalities. In patients who recovered from myocarditis diagnosed by clinical criteria, the incidence of myocarditis on long-term follow-up was 12% (Table 2).[18-25] Since the incidence of dilated cardiomyopathy in the general population is about 7 new cases per 100,000 population per year,[26] the incidence is significantly greater after documented cardiotropic virus infection or clinically diagnosed myocarditis than in the general population. Quigley and colleagues in Great Britain observed for 56 months 23 patients with biopsy-proved myocarditis.[27] Dilated cardiomyopathy developed in 5 of 16 survivors, 5 patients who died, and 2 who underwent cardiac transplantation. In contrast, Sekiguchi and co-workers observed for as long as five years 30 patients in Japan with acute viral myocarditis and histologic confirmation and noted only 2 survivors (8%) with clinical evidence of dilated cardiomyopathy.[28] The difference between these studies may reflect the differing acuteness of the clinical disease.

TABLE 1.—*Evidence of the Role of Myocarditis in Dilated Cardiomyopathy*

Persistent immune responses lead to progressive myocyte damage following viral clearance in a murine model
Patients with dilated cardiomyopathy have exposure to cardiotropic viruses at a greater frequency than controls
Patients who recover from clinically suspected acute viral myocarditis have a higher frequency of dilated cardiomyopathy on long-term follow-up than controls
An immunoregulatory defect in suppressor-lymphocyte function has been documented in patients with myocarditis and dilated cardiomyopathy
Active myocarditis may be seen on biopsy specimens from patients presenting with presumed dilated cardiomyopathy

Despite the controversies, it is clear that dilated cardiomyopathy develops in some patients with active myocarditis, whereas others recover with no residual cardiac dysfunction. Fowles and associates were the first to describe an immunoregulatory defect in suppressor cell function in patients with this disorder.[29] Eckstein and co-workers confirmed this defect and found similar results in patients with active myocarditis.[30] Although not all such patients have demonstrable defects in immunoregulation, it is attractive to hypothesize that an immunoregulatory defect predisposes to persistent immune responses after cardiotropic virus infection in some patients. If so, the host immunoregulatory milieu may be as important in the development of dilated cardiomyopathy as the infection itself. This possibility may account for the documentation of myocarditis in familial cardiomyopathy[31] and the high frequency of myocarditis in women with peripartum cardiomyopathy.[32]

In summary, circumstantial evidence supports the hypothesis that viral myocardial infection leads to autoimmune responses which culminate in chronic myocyte damage, compensatory hypertrophy, dilated cardiomyopathy, and congestive heart failure.

Diagnosing Myocarditis

Before endomyocardial biopsy began to be used in patients with unexplained heart failure, the antemortem diagnosis of myocarditis was solely dependent on clinical criteria. Congestive heart failure of unknown cause preceded by a viral syndrome with an associated fourfold rise in antibody titer to cardiotropic virus was presumptive evidence of myocarditis, particularly if pericarditis or atrioventricular block was present.[33] Mason and colleagues applied the technique of endomyocardial biopsy to patients with heart failure of unknown cause and identified myocarditis in ten.[34] The

TABLE 2.—*Incidence of Dilated Cardiomyopathy Following Recovery From Clinically Suspected Acute Viral Myocarditis*

Source	*Patients, No.*	*Patients With Dilated Cardiomyopathy, No. (%)*	*Duration of Follow-up, years*
Levander-Lindgren, 1965[18]	154	13 (8)	7
Bengtsson and Lamberger, 1966[19]	90	17 (19)	5
Sainani et al, 1968[20]	22	5 (23)	Unspecified
Bergström et al, 1970[21]	15	0 (0)	4
Smith, 1970[22]	22	6 (27)	6
Gerzēn et al, 1972[23]	45	0 (0)	5
Obeyesekere and Hermon, 1973[24]	32	3 (9)	Unspecified
Hayakawa et al, 1983[25]	20	6 (30)	4
Total	400	50 (12)	

incidence of biopsy-documented myocarditis in patients with unexplained heart failure in subsequent reports has varied widely (Table 3).[35-46] This variation cannot be fully explained by geographic differences in the occurrence of epidemics of cardiotropic viruses. A difference in the pathologic interpretation of biopsy specimens is likely the major cause of this discrepancy.

A panel of cardiac pathologists, highly skilled in interpreting endomyocardial biopsy findings, met to establish a working definition of myocarditis to be used in a large multicenter study.[47] They defined "active" myocarditis as the presence of inflammatory infiltration with injury to adjacent myocytes in the absence of coronary artery disease (Figure 1). It is hoped that the publication of these criteria will stimulate cardiac pathologists to apply them or to strictly define their own criteria so that data from various centers may be accurately compared.

Endomyocardial biopsy may be subject to a sampling error in the detection of myocarditis. Although the incidence of a false-negative diagnosis of cardiac transplant rejection is reduced to 2% if at least four adequate specimens are obtained,[48] the frequency with which the endomyocardial biopsy fails to detect active myocarditis is unknown.

Radionuclide techniques in cases of myocarditis have recently been studied in an effort to obviate the necessity of biopsy. Gallium 67, an inflammation-avid radioisotope, is highly sensitive but nonspecific compared with the gold standard of biopsy.[42] The practical limitations of imaging this isotope and the computer processing required to enhance sensitivity make gallium scanning difficult for wide application as a screening tool. Imaging using a murine antimyosin antibody (Fab) labeled with indium 111 has been applied to detect the myocyte necrosis associated with myocarditis and has shown promise as a screening technique in patients with newly occurring heart failure.[49] This technique is also highly sensitive but nonspecific. It has been suggested that the lack of specificity may be due to sampling error of endomyocardial biopsy rather than nonspecific myocardial uptake of the isotope. Nevertheless, myocardial biopsy remains the standard against which other techniques are compared. Both ^{67}Ga and ^{111}In antimyosin antibody imaging must be studied in large trials to ascertain their clinical usefulness in comparison with that of myocardial biopsy.

Figure 1.—A photomicrograph of an endomyocardial biopsy specimen from a patient with unexplained congestive heart failure shows a predominantly lymphocytic infiltrate with necrosis of adjacent myocytes compatible with active myocarditis (hematoxylin and eosin, original magnification × 63).

When patients with active myocarditis were compared with those with possible myocarditis but negative results on endomyocardial biopsy, clinical and hemodynamic variables were not useful in predicting the results of the biopsy.[33] Even an antecedent viral syndrome or elevation of erythrocyte sedimentation rate was not a predictor of the histologic findings or prognosis.

Treatment

Mason and associates reported the results of immunosuppressive therapy in biopsy-documented myocarditis.[34] Five of ten patients treated with prednisone alone or in combination with azathioprine improved. Although this result was better than the authors would have expected in untreated patients, they predicted the need for randomized prospective trials to determine the efficacy of therapy. Numerous investigators have subsequently reported their uncontrolled experience with immunosuppressive therapy in biopsy-proved myocarditis using prednisone alone or in combination with azathioprine, antithymocyte globulin, or cyclosporine.

TABLE 3.—*Incidence of Myocarditis in Patients With Unexplained Congestive Heart Failure*

Source	Location	Patients With Biopsies, No.	Patients With Myocarditis, No. (%)
Mason et al, 1980[34]	Stanford, Calif	400	10 (2)
Nippoldt et al, 1982[35]	Rochester, Minn	34	4 (12)
Fenoglio et al, 1983[36]	New York	135	34 (25)
Hess et al, 1983[37]	Richmond, Va	23	6 (26)
Unverferth et al, 1983[38]	Columbus, Ohio	42	4 (10)
Strain et al, 1983[39]	New York	64	17 (26)
Parillo et al, 1984[40]	Boston	74	19 (26)
Zee-Cheng et al, 1984[41]	St Louis	35	22 (63)
O'Connell et al, 1984[42]	Chicago	68	5 (7)
Dec et al, 1985[43]	Boston	27	18 (67)
Hosenpud et al, 1985[44]	Portland, Ore	38	6 (16)
Cassling et al, 1985[45]	Omaha, Neb, and Indianapolis, Ind	80	2 (2)
French et al, 1986[46]	Los Angeles	25	0 (0)
Total		1,045	147 (14)

TABLE 4.—*Response of Biopsy-Proved Myocarditis to Immunosuppression in Uncontrolled Trials**

Source	Location	Patients: Treated, No.	Patients: Improved, No. (%)
Mason et al, 1980[34]	Stanford, Calif	10	5 (50)
Sekiguchi et al, 1980[50]	Tokyo	3	2 (67)
Edwards et al, 1982[51]	Rochester, Minn	4	2 (50)
Fenoglio et al, 1983[36]	New York	19	8 (42)
Hess et al, 1983[37]	Richmond, Va	6	6 (100)
Daly et al, 1984[52]	London	9	7 (78)
Vignola et al, 1984[53]	Miami, Fla	6	5 (83)
Zee-Cheng et al, 1984[41]	St Louis	11	5 (45)
Dec et al, 1985[43]	Boston	9	4 (44)
Hosenpud et al, 1985[44]	Portland, Ore	6	0 (0)
Mortensen et al, 1985[54]	Copenhagen	12	8 (67)
Salvi et al, 1987[55]	Trieste	17	14 (82)
Total		112	66 (59)

*Data from "acute," "rapidly progressive," and "chronic" pooled.

Overall, 59% of patients improved (Table 4).* The natural history of untreated active myocarditis is unknown, however. It is of interest, in light of the recent finding of viral genomes in biopsy specimens showing myocarditis, that no investigator reported abrupt myocardial deterioration or dissemination of viral infection as a result of immunosuppression.

Randomized Trial

Because of the causal role of myocarditis in the development of dilated cardiomyopathy and the morbidity of inappropriate immunosuppression, a large randomized trial is necessary to ascertain the efficacy of immunosuppressive therapy in myocarditis and to determine whether myocardial biopsy is justified in patients with heart failure of unknown cause. The Myocarditis Treatment Trial, a National Heart, Lung, and Blood Institute-sponsored multicenter study, was developed to answer this question. Eligible patients have unexplained congestive heart failure (an ejection fraction below 0.45) without evidence of coronary artery disease and biopsy-proved "active" myocarditis, confirmed by a panel of pathologists. A total of 23 enrollment centers in the United States, Canada, Great Britain, and Japan, coordinated at the University of Utah, serve as entry points into the study. Patients are randomly assigned to one of two treatment limbs (Figure 2):

Limb 1. Standard conventional therapy for congestive heart failure

Limb 2. Standard conventional therapy for congestive heart failure plus the administration of cyclosporine and low doses of prednisone

In limb 2, cyclosporine was chosen as the primary immunosuppressive agent because it selectively blocks the production of interleukin-2 and has become the cornerstone of immunosuppressive treatment in human solid organ transplantation.[56] With increasing frequency, this agent has been applied to the study of autoimmune diseases such as diabetes mellitus,[57] myasthenia gravis,[58] and rheumatoid arthritis.[59]

*References 34, 36, 37, 41, 43, 44, 50-55.

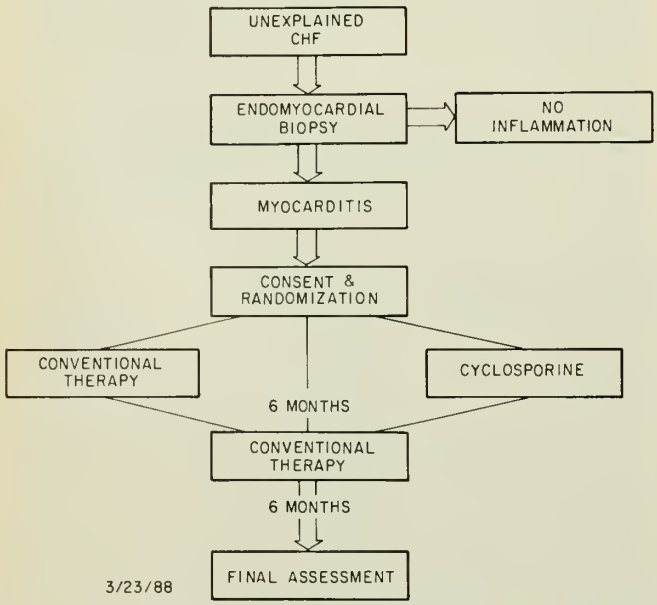

Figure 2.—The study design of the Myocarditis Treatment Trial is shown. CHF = congestive heart failure

Furthermore, it has theoretic advantages over azathioprine in that there is less predisposition to infection with opportunistic organisms and a lesser requirement for corticosteroids in the transplant population. After six months of randomized therapy, the immunosuppressive regimen is discontinued and patients are observed for six months before an end-point evaluation one year from the initial assignment. Primary end points are changes in the radionuclide ejection fraction and treadmill exercise performance.

If referral to a formal enrollment center is not possible, an abbreviated protocol is available for any patient with biopsy-proved myocarditis in any center in the United States where treadmill exercise testing and radionuclide ventriculography are available. When a patient has biopsy-proved myocarditis and is considered for a random assignment of therapy, the referring physician should contact one of us at (800) 441-5544 or (801) 581-7715. The pathology slides will be directed to a member of the pathology panel for diagnostic confirmation. After informed consent and documentation of a left ventricular ejection fraction of less than 0.45 by radionuclide ventriculography, the patient will be randomly assigned. If assigned to limb 2, the cyclosporine will be provided by the coordinating center. It is expected that this open-enrollment phase of the trial will accelerate patient acquisition and, hence, allow conclusions to be reached at an earlier time. This trial will be actively recruiting patients through 1990, and 200 patients will be randomly assigned by completion of the trial.

In addition to the clinical trial, this study involves assessing cell-mediated immune responses including characterizing the cells infiltrating the myocardial biopsy specimens, the subpopulations of cells in the peripheral blood, suppressor cell function, antibody-dependent cellular cytotoxicity, and natural killer cell activity. Humoral immune responses are measured by determining the presence of heart reactive antibody and specificity of the antibody for myocyte antigens such as myosin. In situ hybridization to detect enteroviral genomes is done on myocardial biopsy specimens with positive results and compared with a control group so that the role of the humoral and cellular arms of the immune system and the persistence of infective agents can be estimated. If the trial shows that active myocarditis responds to immunosuppressive therapy, it will be recommended that all patients fitting the profile of those who responded to therapy undergo myocardial biopsy and, if myocarditis is found, receive a trial of immunosuppression.

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Specialty Conference

Effects of Transplacental Exposure to Cocaine and Methamphetamine on the Neonate

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SUZANNE D. DIXON, MD*: Experience at the University of California, San Diego (UCSD), Medical Center with the consequences of the abuse of cocaine and methamphetamine in pregnancy is substantial and increasing. The implications for infants with in utero exposure to these drugs are becoming clearer from our own recent clinical experience and that of others. In this conference I will review what is known about antenatal exposure to these drugs and present some recent observations and experience.

Patterns of Exposure

The clinical urgency of these considerations is highlighted by the incidence of infants born at UCSD over the past four years in whom illicit drugs have been found by toxicologic assessment of the urine at birth. There was a 35% increase from 1984 to 1986 (Figure 1).

Since then there has been an almost fivefold increase in the incidence. These numbers do not include infants in whom there was exposure early in gestation or those from whom the drugs cleared before birth. Therefore, these numbers vastly underestimate the full extent of the problem. Similar increases have been reported from virtually every major urban center. For example, Los Angeles County reported a doubling every year since 1983 of the number of infants born with illicit drugs in their urine. Other centers cite the incidence of this problem at 10% to 25% of neonates. These increases in rates are accounted for largely by an increase in the use of stimulant drugs, cocaine, methamphetamine, and, to a lesser extent, hallucinogens such as phencyclidine hydrochloride.

It is estimated that 50 million Americans have tried cocaine and that 8 million use it regularly. Between 10% and 20% of the adult population uses some nonprescription, psychoactive drug regularly. By one estimate, 12% of young adults have severe addictive disease. Although the increasing use of alcohol and other drugs among adolescents is a major concern and the target of educational programs, most drug users are 20 to 35 years of age, the childbearing years. The greatest increases in drug use starting in the 1970s and accelerating in the 1980s are among young adults. The perinatal impact of this issue is a direct result of the broad increase in drug use in this segment of the population.

The pediatric community was unprepared for this epidemic in our nurseries. Reports of the effects of cocaine on adults began to emerge after 1982 and exploded onto the pages of the popular press. The effects on the fetus were largely unknown. Reports of the consequences of amphetamine exposure on the unborn were few. The only available model in pediatrics was our experience with neonates having exposure to opiates. The course of withdrawal and outcome for heroin- and methadone-exposed children has been well described, for instance, by Volpe.[1(p616)] The signs of neonatal narcotic withdrawal are quantified in scoring formats such as that developed by Finnegan.[2(p262)] Although these schemes allow us to monitor and treat neonates who have exposure to opiates and other central nervous system (CNS) depressants, this familiar approach could not readily be applied to these new stimulant drugs and their new multiorgan effects.

History of Cocaine Use

Cocaine (Figure 2) is derived from the *Erythroxylon coca* plant grown in the mountains of Latin America. The leaves of this plant have been chewed by members of Indian tribes for perhaps 5,000 years to abate hunger and improve work endurance. Cocaine was isolated and introduced to northern industrial countries in 1859. Fans of Sherlock Holmes know the role the drug played in his creator's life. Freud praised the stimulant properties of the drug despite the fact that he lost a friend and patient to a toxic overdose. Coca Cola contained the drug until 1903. By 1906 awareness of the toxic potential of cocaine led to restricted access, with its being used primarily as an anesthetic for ear, nose, and throat and ophthalmologic operations. Recreational users were few in number and usually wealthy, as the drug was expensive. A resurgence in the popularity of cocaine began in the 1970s, but the astronomic rise in its use in this country occurred in 1982, along with a dramatic increase in illegal imports. The newspaper and television reports of the deaths of prominent athletes and entertainers brought to almost every household an awareness of this drug and its toxic consequences.

A primer on cocaine is given in Table 1.

Pharmacology of Cocaine

The powerful euphoric effects of cocaine depend largely on the CNS release of dopamine, which is followed by depletion of that compound, leading to the "crash" or abstinence syndrome characteristic of this drug. Cocaine also facilitates the release of serotonin and other neurotransmitters.[3] It has

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
UCSD = University of California, San Diego

been described as a uniquely American drug that imparts a sense of power, increased self-esteem and vigor, decreased fatigue, and an increased sense of sexual prowess. Hypersomnolence, hyperphagia, irritability, and depression are the down side of the cocaine cycle. Investigators now accept cocaine as a physically addictive drug, particularly when taken in high concentrations, such as with "crack" or "rock" cocaine.[4]

In addition, cocaine blocks the presynaptic reuptake of norepinephrine and increases the amount of that substance at postsynaptic receptor sites throughout the body. Over time, there is a net depletion of norepinephrine. There is an increase in the activity of the sympathetic nervous system, a decrease in peripheral nerve conduction, and direct action on some smooth muscle groups.

The toxic effects follow from this pharmacologic action (Table 2). The most important effect of this drug is powerful vasoconstriction. Essentially every organ system is vulnerable to this vasoconstrictive action. The cardiac effects have received the most press, but multiple organ systems show the toxic effects of this drug.[4]

The plasma half-life is about 30 to 40 minutes. The drug is detoxified by cholinesterases in plasma and liver. The plasma enzyme has wide individual variation, which may account for the variable and unpredictable toxicity of cocaine. Cardiac morbidity appears to be unrelated to the dose, duration of usage, underlying disease, or route of administration. This unpredictability makes cocaine a dangerous drug; it dissolves some popular myths regarding cocaine, such as "snorting the drug is OK; smoking and inhaling it is not"; "I use it only at parties, so I'm safe"; "cocaine is not addictive; it's easier to kick than heroin." Of importance for pediatricians is that the activities of cholinesterases are at relatively low levels in pregnant women, fetuses, and newborns. As a group, perinatal patients might be predicted to be more vulnerable to the toxic effects of this drug.

Cocaine is metabolized to benzoylecgonine and ecgonine, distinct substances that can be identified by several commonly used toxicologic assessments. Immunoassay of the urine may give positive results as long as five days after use in nonpregnant adults.

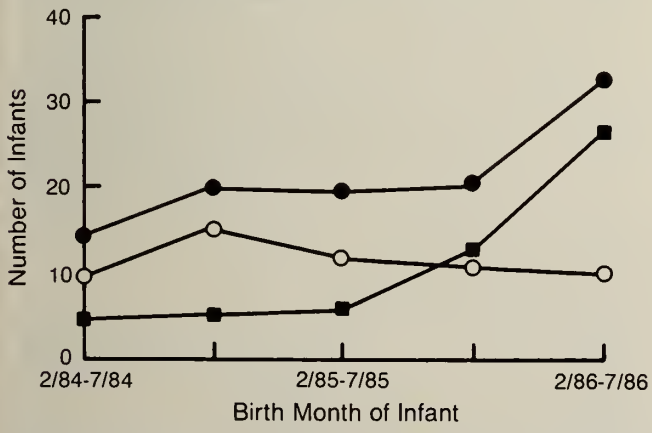

Figure 1.—Patterns of drug exposure are shown for infants born at the University of California, San Diego, Medical Center from 1984 to 1986. ● = total documented drug-exposed infants, ○ = infants with narcotics exposure, ■ = infants with stimulants exposure

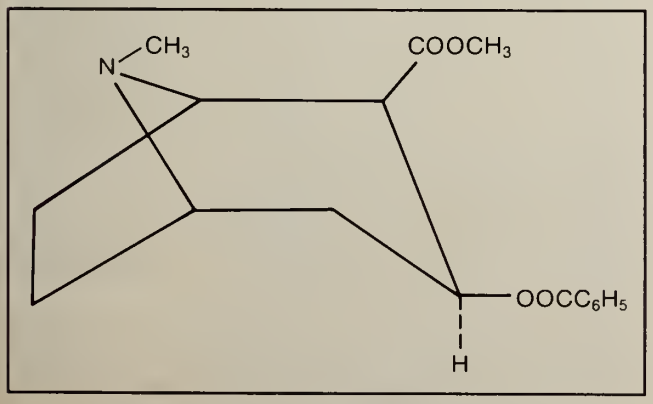

Figure 2.—The structure of cocaine is shown.

TABLE 1.—*Cocaine Primer*

- Derived from leaves of *Erythroxylon coca*
- Imported as a white powder, often mixed with talc, lactose, or dextroamphetamine sulfate
- Simple molecule, easily absorbed across any membrane for use intranasally, intravenously, intramuscularly, subcutaneously, orally, sublingually, intravaginally, intrarectally; present in breast milk
- Easily made into hydrolyzed crystal—"crack," "rock"—that is easily vaporized—"smoked"—with rapid absorption and high concentration; this form is rapidly and strongly addictive
- Although cheaper by the dose, the duration of the high with "crack" is brief and the addictive potential high
- Street names: "coke," "snow"; when combined with heroin, "speedball"
- Often used with depressants, alcohol, or heroin
- Produces euphoria, increases activity and gregariousness; reduces appetite and sleep
- Metabolized to benzoylecgonine and ecgonine and detectable in urine for as long as 5 days in the average nonpregnant adult

TABLE 2.—*Clinical Consequences of Cocaine Use in Adults*

Cardiovascular
- Hypertension, tachycardia
- Cerebral infarction
- Nonthrombotic myocardial infarction
- Ventricular arrhythmias
- Subarachnoid hemorrhage
- Ruptured aneurysms, peripheral and central nervous system
- Aortic rupture
- Renal infarction
- Bowel infarction
- Chronic colitis
- Dermatitis, presumably related to small vessel disease

Central Nervous System
- Euphoria, increase in activity, and increased sense of creativity and sexual prowess
- Psychosis, hallucinations
- Depression
- Seizures
- Respiratory arrest
- Labile affect, panic disorder, aggressive ideation and behavior
- Decreased total sleep and selective reduction of rapid-eye-movement sleep

Other
- Fever or malignant hyperthermia
- Anorexia
- Midriasis
- Perforated nasal septum
- Infectious disease risk associated with life-style issues and, in a minority, intravenous use

Complications of Cocaine Use in Pregnancy

Studies in animals carried out at UCSD and elsewhere have revealed decreases in uterine and placental perfusion and a direct increase in uterine contractility following the administration of cocaine.[5] Observations in women are consistent with these findings. There are sharp increases in fetal wastage, increases in the incidence of placental abruption, and precipitous onsets of labor following cocaine use. In one study of otherwise healthy "recreational" users of cocaine in Chicago, Chasnoff and co-workers noted a 23% spontaneous abortion rate.[6] A comparison of the histories of pregnant women using drugs indicated an incidence of spontaneous abortions among users of cocaine more than twice that of a group of users of heroin (38% versus 16%). The mean number of previous spontaneous abortions was also increased in the cocaine-using group (0.98 to 1.1 versus 0.47 to 0.9). The highest fetal wastage was among cocaine and heroin users: 46% reported a previous spontaneous abortion, and the mean number was 1.3 to 1.2 per woman. Data from our Teratogen Registry at UCSD indicate a 28% spontaneous abortion rate among women calling early in pregnancy because of concern about their self-described "recreational" cocaine use (K. L. Jones, MD, oral communication, 1987).

Increased systolic blood pressure, decreased uterine and placental perfusion, and increased uterine contractility may all contribute to the consistent observation by several investigators of about a tenfold increase in the incidence of placental abruption, hemorrhage, or both associated with cocaine use.[4-6] There are several clinical reports of the immediate onset of contractions after cocaine administration, and our own clinical interviews support this. Street lore supports the notion that cocaine use "starts the baby"—that is, starts labor.

A study in sheep suggests that cocaine administered to ewes results in more fetal distress than the direct intraamniotic administration of the drug to the fetal lamb.[7] The decreased placental perfusion and resultant anoxia in the fetus may be more detrimental than direct effects of the drug.

An interesting study from Northwestern University Medical School (Chicago) showed alterations in placental neurotransmitter receptors in tissue obtained from drug-using women. The supposition is that these alterations reflect similar chronic changes in the fetal brain. Although preliminary and based on a study of polydrug users, the findings suggest important opportunities for research aimed at assessing neurotransmitter systems in the developing brain. In that study, the most deviant values were seen in the placenta from a stimulant drug-using woman, presumably due to the direct alteration in the neurotransmitter system associated with these drugs.

Neonatal Consequences of Cocaine Use

Cocaine crosses the placental barrier by rapid simple diffusion. A variety of skeletal defects, exencephaly, hydronephrosis, and cryptorchidism, were described by Manhalik and colleagues in a mouse model of antenatal cocaine use.[9] In a clinical report from New York, skull defects were identified in a number of infants, and there was an increase in the incidence of congenital heart disease among a group of urban minority-group neonates.[10] Chasnoff and Chisum reported three instances of the prune-belly syndrome,[11] one they related to a single large maternal dose of cocaine taken at five weeks' gestation,[6] a critical time in the development of the urinary tract. They also reported a 13% incidence of obstructive uropathy in this group with mild hydronephrosis, and, of 81 infants studied prospectively with renal ultrasonography, 6 had hypertension. No child has yet been noted with any long-term alteration in renal anatomy or function. We have not seen this in more than 100 infants studied, although transient hypertension frequently occurs.

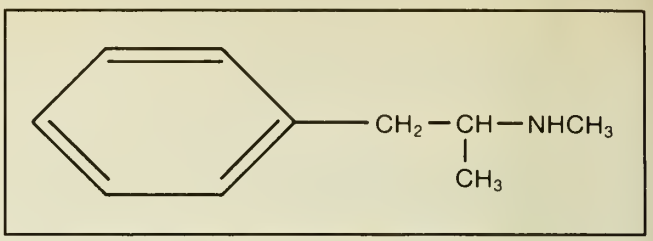

Figure 3.—The structure of methamphetamine is shown.

There is a growing consensus that cocaine produces intrauterine growth retardation and, in particular, a reduction in brain growth. In a recent report,[12] altered lymphocyte function was noted among infants born of human immunodeficiency virus-negative intravenous drug abusers, 44% of whom used cocaine and amphetamines.

Acute cerebral hemorrhagic infarction,[13] white matter cavitary lesions, and other abnormalities were identified by cranial ultrasonography in 12 (37%) of 32 cocaine-exposed neonates.[14] Two instances of myocardial infarction have been identified in cases of immediate antenatal usage. We have seen two term infants with an acute infarction of the bowel at birth, possibly related to maternal usage of cocaine.

Cocaine readily crosses into breast milk, with adverse consequences for the newborn child.[15,16]

In summary, these reports do not appear to support a concept of distinct embryopathy related to cocaine use. Multisystem abnormalities of a variety of types might be anticipated, in view of the vasoconstrictive properties of this drug, the variability depending on the dosage, the time of exposure in relation to fetal development, and individual variation.

Methamphetamine Use

The first cousin of amphetamine, methamphetamine (Figure 3), enhances the presynaptic release of norepinephrine, alters CNS neurotransmitters, and in these respects has pharmacologic effects nearly identical to those of cocaine.[3] It is excreted unchanged and as amphetamine for as long as two days after its use in adults. Immunoassays for this drug are confounded by its cross-reactivity with a variety of drugs, including cold remedies and tocolytic agents. Amphetamine use in adults results in central nervous system excitation, followed by a withdrawal period characterized by prolonged sleep, lassitude, fatigue, hyperphagia, and vivid dreams. Long-term use is associated with an aggressive paranoid psychosis and a pattern of deep-brain strokes. Vasospastic strokes, ruptured cerebral aneurysms and infarctions around the basal ganglia, and a cerebral angiitis are seen in cases of adult amphetamine use. Lead poisoning related to manufacturing techniques has also been reported as a complication of methamphetamine use in adults. A primer of methamphetamine is provided in Table 3.

Methamphetamine is the most commonly abused drug in San Diego County. It accounts for 33% to 40% of referrals to treatment centers and represents more than 60% of seizures of illicit drugs by law enforcement. Other rural or semirural

areas are also experiencing an increase in the use of this "homegrown drug."

Amphetamine Use in Pregnancy and the Neonatal Period

The methyl radical has been added only recently, and previous medical reports of illicit amphetamine use are primarily of intravenous use. In the 1950s obstetricians prescribed low oral doses of amphetamine to reduce weight gain in pregnancy; no structural abnormalities were found in those children. In 1974 Ramer described an infant with exposure to illicit amphetamine who had hypoglycemia, sweating, poor feeding, and poor visual tracking with deviations of the eyes.[17] The infant had periods of having a dusky color and had a "glassy-eyed" appearance. A clinical seizure in the absence of electroencephalographic changes was noted on day 6 of life. The child was described as normal at 2 years of age, but no detailed neuropsychological tests were reported.

The largest series of observations has come from the Karolinska Institute in Sweden.[18] Infants reportedly were born to two groups of mothers, one of which stopped the intravenous use of amphetamines during their pregnancies, while the other continued using the drug throughout. There was an increased incidence of morbidity in both groups, but problems were more severe in the group that continued to use the drug. Alcohol use was high in both groups. There was an increase in the incidence of preterm labor, placental abruption, fetal distress, and postpartum hemorrhage. Normal somatic growth was noted by one year despite an increased illness and accident rate in these groups. The infants with continued exposure were smaller and had feeding difficulty to the point of requiring gavage feedings. Drowsiness and lassitude lasted several months in these infants. Development was described as "very slow" for six months for those infants who went to foster homes and presumably received better care and observation. The foster mothers often suspected hearing loss, but none was found. Perhaps they were responding to a decreased quality of alertness in those children.

TABLE 3.—*Methamphetamine Primer*

- Produced locally in stills using simple chemicals, primarily ephedrine
- White powder that is taken intranasally (rarely by injection), with the rapid onset of a "high"
- Regularly used with large amounts of alcohol or other depressants
- Street names: "crystal," "crystalmeth," "speed"
- Chronic user: "speed freak"—usually indicates chronic psychiatric impairment
- Metabolized to amphetamine and identified in urine for 1 to 3 days in an average adult
- Cross-reacts in immunoassay with antihistamines and other cold remedies and tocolytic agents
- Has been associated with cardiovascular morbidity, acute psychosis, malignant hyperthermia, and hypertension
- Ruptured cerebral aneurysms, basilar brain infarctions, cerebral angiitis, and other intracerebral hemorrhages also occur

The San Diego Experience

In a retrospective analysis of our own experience in San Diego from 1984 to 1986,[19] we compared the perinatal courses of infants in whom cocaine or methamphetamine was present in the urine at birth. This presumably represents a population in whom there was relatively high or prolonged drug exposure, although precise drug use data are inaccurate in almost all clinical settings. Regarding maternal medical factors, we found that the two groups showed no significant differences (Table 4). Both groups consisted of women in their mid-20s, usually with other children; less than 5% were younger than 21 years. There was an increase in the incidence of placental abruption in both groups. Most of the women received no or limited prenatal care.

The neonatal outcomes were also comparable in the cocaine- and methamphetamine-using groups: intrauterine growth retardation, decreased head circumference, preterm

TABLE 4.—*Maternal and Neonatal Morbidities Associated With Cocaine and Methamphetamine Use in Contrast to a Medically and Demographically Similar Control**

	Drug Use			
Demographics	*Cocaine, n=13*	*Methamphetamine, n=28*	*Control, n=45*	P
Maternal				
Maternal age, years	26.1±4.8	24.1±4.6	25.8±5.9	NS
Gravidity	3.7±2.6	3.2±1.5	3.3±2.1	NS
Parity	1.7±1.1	1.6±1.0	2.1±1.4	NS
Abortion	2.0±1.8	1.6±2.5	1.2±1.4	NS
Prenatal care				NS
Complete, %	0	0	7	
Limited, %	69	57	64	
None, %	31	43	29	
Nicotine use, %	38	31	...	NS
Ethanol use, %	46	20	...	NS
Neonatal				
Gestational age, weeks	37.5±3.1†	38.1±3.1‡	39.4±1.4	.01
Birth weight, grams	2,719±739†	2,955±710	3,246±522	.02
Length, cm	47.6±4.9†	48.1±5.7‡	50.7±2.8	.02
OFC, cm	32.6±2.8†	33.2±2.1‡	34.3±1.5	.006
Apgar score				
1 min	7.8±0.6	7.4±2.1	8.0±2.0	NS
5 min	8.8±0.4	8.4±1.5	9.0±1.0	NS

NS=no significance, OFC=occipitofrontal circumference

*Except for percentages, values are the mean ± standard deviation.
†$P<.05$ Cocaine versus control groups.
‡$P<.05$ Methamphetamine versus control groups.

delivery with fetal distress, and anemia were common in both groups.

The withdrawal course, as monitored by the Finnegan scoring system,[2] was abnormal in similar ways; CNS symptoms predominated. Most infants had symptoms that included abnormal sleep patterns (81%), tremors (71%), hypertonia (52%), high-pitched cry (42%), poor feeding (58%), vomiting (51%), sneezing (45%), frantic sucking (42%), and tachypnea (18%) (Figure 4). Three methamphetamine-exposed infants required gavage feeding because of lethargy and poor feeding.

In comparison to a narcotic-exposed group, the combined stimulant group, including infants with exposure to both cocaine and methamphetamines, had similar reductions in intrauterine growth and less severe abstinence scores.

In comparison to an economically, racially, and sociologically comparable drug-free group, all the neonates with drug exposure had more adverse perinatal outcomes and a higher incidence of preterm delivery, lower birth weights and head circumferences for gestational ages, and a higher rate of anemia (Table 5). Indeed, when all the perinatal features, including adverse demographic and economic factors, were analyzed using a multiple regression format, only drug exposure contributed statistically significantly and adversely to intrauterine growth and gestational age in both the cocaine- and methamphetamine-exposed groups. This effect seems to be over and above the deleterious effects of poverty, poor nutrition, and a lack of prenatal care that always confound the clinical situation.

Between January 1987 and July 1988, we have seen 103 new term infants with exposure to the following drugs: cocaine, 41%; methamphetamine, 30%; opiates, 8%; and combined cocaine and heroin, 22%. During this time, essentially all of the heroin users also used cocaine, which is a new trend. This is consistent with the data from New York, where 36% of "compliant" methadone users and 80% of heroin users also used cocaine. This means that even that old familiar group, narcotic-exposed neonates, will be more challenging because of this combined exposure. In this "speedball" group, the morbidities were of the same variety, only more severe: prematurity rate, 45%; small for gestational age, 46%; and reduced occipitofrontal circumference for gestational age, 29%. Withdrawal is more prolonged and severe in this group, and the mothers are farther away from recovery.

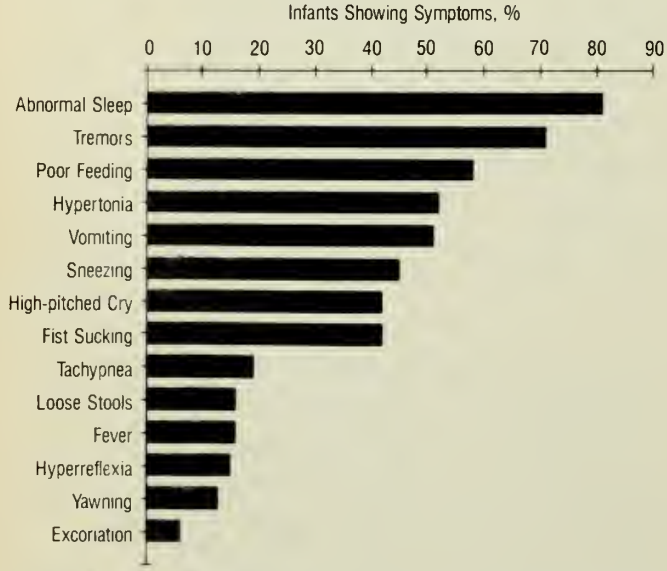

Figure 4.—The graph shows the neurobehavioral symptoms seen in neonates with exposure to stimulant drugs. Most infants showed some abnormal neurologic and physiologic behaviors suggestive of drug effect or withdrawal.

TABLE 5.—*Perinatal Morbidities of Drug-Exposed Infants, %*

Perinatal Morbidity	*Stimulants,* n=46*	*Narcotic, n=49*	*Control, n=45*
Prematurity	28†	22‡	9
Small for gestational age	9	9	2
Small head circumference for age	17	17	4
Fetal distress	39	38§	24
Bradycardia	22	24	17
Meconium	17	11	7
Placental hemorrhage	13†‖	2	2
Anemia	13†‖	2	0
Seizure	2	8	0
Cerebral infarction	2	0	0

*Cocaine and amphetamines.
†$P<.05$ Stimulant versus control groups.
‡$P<.05$ Narcotic versus control groups.
§Three infants had variable deceleration.
‖$P<.05$ Stimulant versus narcotic groups.

Demographically, the cocaine and methamphetamine users are distinct groups. The cocaine users tend to be of inner-city minority groups, initially all black but now 25% Hispanic. They are Medi-Cal recipients but rarely have sought access to care. In contrast, users of methamphetamine in San Diego are predominantly white and come from all areas of the county, including semirural areas. They have no health coverage, have high unemployment rates, and are largely outside of systems of care. These are angry, aggressive, difficult parents who have strong denial mechanisms and chaotic life-styles. The cocaine-using parents are either so locked in by drug abuse that they are unable to care for their infants or they present with management problems common to poor, inner-city minority families. The newly emerging group of Hispanic women appears to be recently recruited to the drug scene through cocaine. Heroin is used as a secondary drug to dampen the "crash" of cocaine. Although phencyclidine use is growing among Hispanic communities, we have seen little of that in our neonates. In contrast, infants with exposure to phencyclidine are common in Los Angeles County.

Our clinical observation indicates that the abstinence scoring derived from the narcotic model does not capture the full range of behavioral alterations seen in infants with exposure to stimulant drugs. A series of Brazelton Neonatal Assessment Scale examinations were initially done on 15 infants with exposure to cocaine and now on a larger sample of 60. These studies have indicated a pronounced alteration in visual processing, quality of alertness, tremulousness, and startle reflex. Abnormalities of a similar but less dramatic nature had been reported by Chasnoff and associates.[6] Children with exposure to methamphetamine showed similar but less severe alterations in newborn behavior in this examination.

The visual system appeared particularly impaired after exposure to either stimulant drug. Flash-evoked visual potentials were assessed in 17 cocaine-exposed infants[20] and were abnormal in the vast majority. In subsequent studies, 62 (78%) of 80 had abnormal visual potentials, and more than

half remained abnormal through the first year. The long-term outcome is unknown.

Several mechanisms could account for this. First, visual processing as a sophisticated system in neonates may be more sensitive to a more generalized neurophysiologic disturbance. Second, changes in retinal and conjunctival vasculature have been described in adult users and passively exposed infants. We have not seen retinal changes in the infants assessed so far, but a prospective study is clearly needed. Third, certain areas of the brain coordinating visual processing may be particularly affected, either through vasoconstrictive necrosis in, for example, the frontal lobes or through alterations in neurotransmitters. These mechanisms are speculative at this time.

Electroencephalographic changes were noted in this population[19] that consisted of an increase in positive sharp wave activity, particularly in the frontal and central vertex regions, and an increase in the wave activity. These are suggestive but not diagnostic of white matter disease. Four children were found to have seizure discharges, evident clinically only by a substantial decrease in alertness. A pronounced alteration in sleep-wake cycles was seen in the majority of children.

Following the report of neonatal stroke, we began to look at ultrasonographic examination of the brain.[14] One cocaine-exposed infant appeared to have had a similar cortical wedge lesion that occurred before birth. This was confirmed by a computed tomographic scan that also showed diffuse white matter attenuation suggestive of previous ischemic damage. A third of the 74 term infants studied, who were otherwise entirely well, have had evidence of brain hemorrhage, cavitation, or infarction commonly involving the basal ganglia around the internal capsule or deep in the frontal lobes, atrophy, or major hemorrhage in the posterior fossa. The evolution of these perinatal infarcts is shown in ultrasonographic images in Figure 5.

Computed tomographic and magnetic resonance imaging scans show diffuse cerebral atrophy or what appears to be delayed myelination. The small size of these lesions may require further refinements of imaging techniques. Areas of infarction and cystic change on cranial ultrasonograms are distinct from the hemorrhagic periventricular leukomalacia seen in preterm infants that may be the antecedent of classic spastic diplegia. These areas appear to be functionally "silent" in the newborn period as the location of these lesions is distinct.

Follow-up Studies

This population of children is extremely difficult to follow up, and there are no large long-term studies of physical and behavioral development of neonates with exposure to stimulant drugs. In our own experience, 59% have gone to foster homes initially. At the end of one year, about 30% have

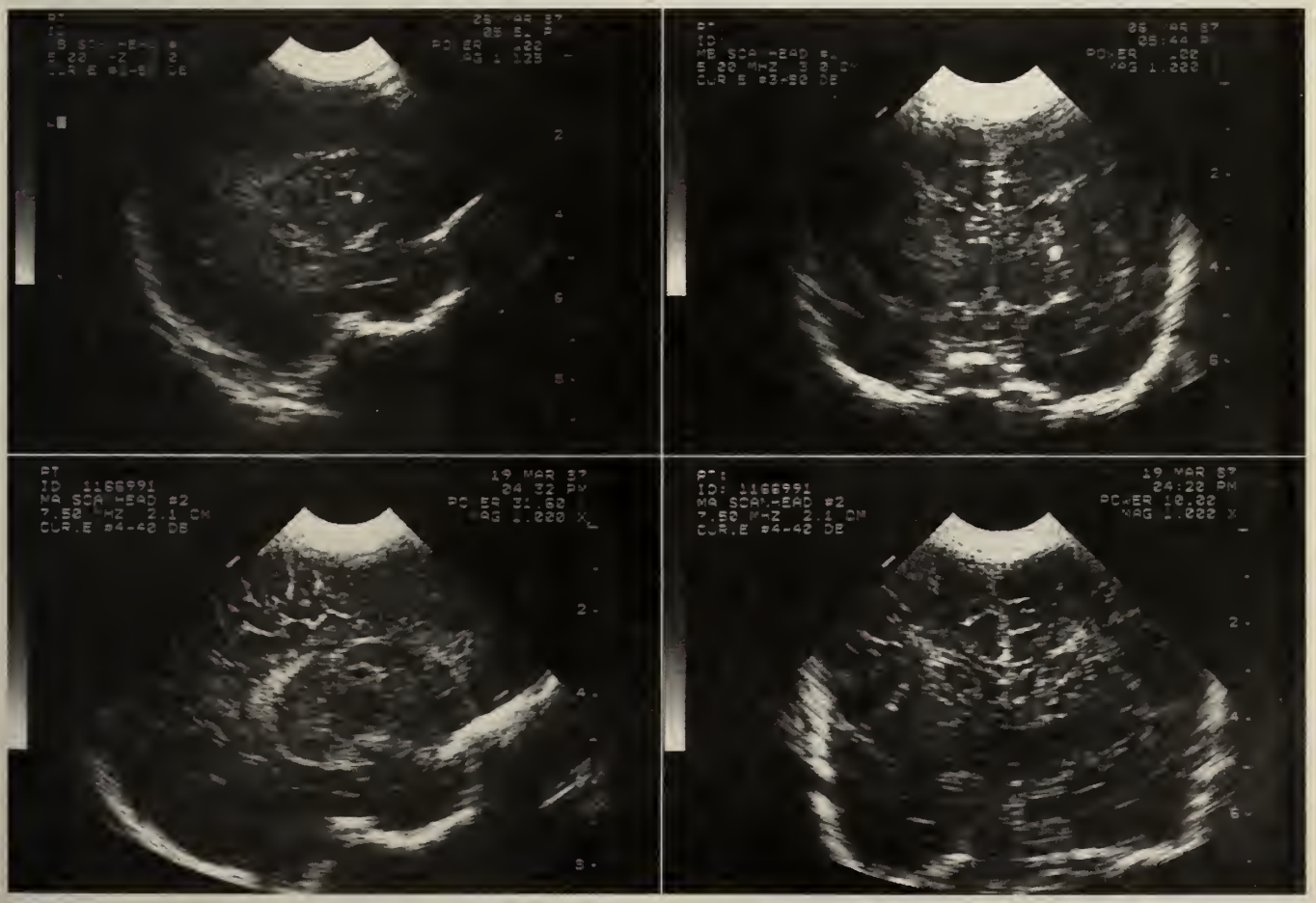

Figure 5.—Upper left, A parasagittal cranial ultrasonogram on day 1 shows an area of hemorrhage (round white lesion) at the base of the brain. **Upper right,** A coronal section taken of the same infant on day 1 of life validates the area of acute hemorrhage inferior and lateral to the lateral ventricles. **Lower left,** A parasagittal study on day 14 of life shows that the hemorrhagic area seen in the initial study has now become cystic (dark) and other echolucent areas are seen around it. **Lower right,** The coronal view also shows the cystic infarctions on day 14 where hemorrhage was seen earlier.

remained in foster care, but two to three shifts of homes is common. For infants who go home with their mothers, chaotic life-styles continue, even if drug use by the parents is eliminated. Recidivism for treated chemically dependent parents remains high.

Developmental assessments of our population have shown that about three fourths have developmental quotients of less than 100 during the first year, with areas of fine motor and visual motor coordination showing the greatest delays. In these areas there is a decrement of performance related to age in a cross-sectional group of these children. Fine motor development appears more compromised as the children mature, compounded by the fact that more fine motor items are assessed at older ages. This observation is consistent with our clinical impression that visual-motor coordination is selectively impaired in both cocaine- and methamphetamine-exposed neonates. More formal analysis is in progress. As a group, however, these children certainly warrant close developmental assessment, particularly as the structural brain lesions are concentrated in areas that may not show impaired function until school age.

Infants with exposure to cocaine apparently go through a secondary withdrawal phase of neurobehavioral disturbance at 2 to 8 weeks of age. They are extremely irritable, hypertonic, sweaty, mildly febrile (38°C [100.2°F]), hyperphagic, and have notable decreases in sleep. Typically the weight not only catches up but becomes excessive. The usual supportive measures, including pacifiers and rocking, that are used for narcotic-exposed infants appear ineffective. About 25% of these children have been treated with phenobarbital, regardless of the source of the primary care prescriber, and it was reported that sleeping and eating patterns improved.

Foster parents have described these infants in vivid terms: "He shakes all the time, even when he sleeps." "He just sweats; he goes hard at things." "She hates the world; she's so angry." "I can't stop him from eating—nothing else works." "He keeps the house up all night." "Holding her doesn't seem to help." "This is the worst drug kid I've had."

In this group, we have seen children with spastic quadriparesis, hemiplegia, microcephaly, global delay, and seizures. We have also seen an 8-month-old infant whose hyperactivity was to such a degree that the administration of methylphenidate was suggested by two other providers. A turbulent neonatal course appears to be associated with a more severe subacute withdrawal phase. It is in this group that the most severe neurologic impairments occur.

In contrast, methamphetamine-exposed infants as a group appear less impaired in the first year. They exhibit lethargy, poor feeding, poor alertness, and severe lassitude. They are described as follows: "Her eyes are glassy." "He forgets to suck while I'm feeding him." "He stares up at his mobile, but I don't think he follows it." "She's such a good baby—she never cries." "She's very quiet." "Her eyes are blank." Most of these children have minor neurologic abnormalities, but development is usually within normal limits during the first year. Three infants have been readmitted with medical problems compounded by severe neglect. Some of the most severe, unusual, and surprising outcomes have been seen in this group, however. Prediction from perinatal findings is poor. Oculomotor apraxia, a parkinsonian dystonia, a severe tactile-elicited dystonia, pronounced intention tremor, severe active hypotonia, and a hemiparesis developed in children in this group after a relatively benign neonatal course. Many of the abnormalities suggest frontal lobe dysfunction that may only be manifested at school age. Severe visual motor difficulties were noted in two otherwise normal preschoolers who were known to have had antenatal exposure to methamphetamine.

Conclusion

Neonates who have had exposure to cocaine or methamphetamines are with us in ever-increasing numbers. They challenge every child care provider in health, education, and in the social and legal systems. The hold of chemical dependency on parents makes it difficult for them to meet the needs of these children without an expansion of existing treatment facilities. The foster care system is vastly overburdened. We have reason for very major concerns about the outcome of this population. In contrast to heroin and methadone—which are detrimental to children also—these drugs have the potential for serious structural damage to the central nervous system that has implications for long- and short-term development. Although many infants present challenges in the first year of life, others may emerge only at school age with handicaps that impinge on their development. By comparison, this epidemic will make the one of neonatal narcotic exposure seem a simpler and less disabling disorder.

New techniques of neuroimaging, increasing sophistication in neurobehavioral assessment, and advances in neurochemistry can be integrated into new understandings of the structural and functional relationships in the developing brain in this clinical population, as we attempt to cope with and eradicate this horrible human experiment.

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Medical Staff Conference

The Pulmonary Complications of Bone Marrow Transplantation in Adults

Discussant
PAUL W. NOBLE, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Bone marrow transplantation is increasingly promising in the management of patients with hematologic and some solid malignant disorders. Unfortunately, pulmonary complications often develop in the weeks or months after transplantation and carry a substantial mortality. I am pleased to have our medical chief resident, Paul Noble, MD, review the experience at the University of California, San Francisco (UCSF), with its first bone marrow transplants.*

PAUL W. NOBLE, MD†: Bone marrow transplantation has evolved from an experimental salvage therapy for patients with hematologic malignancy offered only at a few centers to an accepted approach in the treatment not only of acute and chronic leukemia but of lymphomas, selected solid tumors, and a variety of nonmalignant conditions. Complications of the cytotoxic preparative regimens, the immunologic sequelae of engraftment, and infections resulting from immunosuppression account for most of the mortality associated with marrow transplantation. These complications can manifest in various forms, and the pulmonary system is a frequent site of involvement. As attested by the adult marrow transplant unit at UCSF, transplant units are developing at an increasing rate, and more and more physicians will need to become familiar with the care of patients having this procedure and with the difficult decisions in the management of pulmonary complications of transplantation.[1] In this conference I report on the pulmonary complications of the first 57 adult bone marrow transplants done at UCSF, with special reference to pneumonia, respiratory failure, and mechanical ventilation. I also discuss methods of diagnosis and treatment.

Pulmonary Toxins and the Conditioning Regimen

Before receiving a donor marrow infusion, the bone marrow of the recipient must be prepared with a conditioning regimen. The purpose of the conditioning regimen is threefold: to create space in the patient's marrow for the expansion of progeny from the stem cells provided by the donor, to enhance engraftment by suppressing immunologic resistance in the recipient, and to eradicate malignant cells.[2] Marrow transplantation allows for the administration of higher doses of chemotherapy than do induction protocols because infusion of the donor marrow provides a hematologic "rescue" that would otherwise not be possible. These regimens vary from center to center but generally involve combinations of chemotherapy and irradiation. Many of the agents used have potential pulmonary toxicity.[3] Cyclophosphamide, busulfan, cytarabine hydrochloride, and total body irradiation are used most often, and all have been implicated in causing pulmonary toxicity. Several animal models suggest that irradiation is more important than chemotherapy in causing interstitial pneumonitis,[4] but because of the confounding variables interacting after marrow transplantation, such as graft-versus-host disease and infection, it is difficult to sort out the contribution of each modality to pulmonary dysfunction. Chemotherapy-related pulmonary damage may be dose-related and can occur anytime after administration.[5] Diffuse pulmonary infiltrates, fever, cough, and dyspnea are accompanied by hypoxemia, decreased diffusing capacity, and reduced lung volumes. The identical clinical picture is produced by irradiation, and, unfortunately, in both cases the histopathologic features are nonspecific. The initial insult is felt to be to the endothelium with resulting interstitial and alveolar edema, destruction of type I pneumocytes, and, later, type II pneumocyte proliferation and fibrosis.[6] With irradiation, injury is clearly dose-related, and fractionation rather than single-dose administration appears to reduce lung toxicity.[7] At UCSF, 12 Gy (1,200 rad) is delivered in six fractions before the marrow infusion.

Methotrexate and cyclosporine, agents used as prophylaxis against graft-versus-host disease, have also been suspected of causing pulmonary damage.[3] Methotrexate may predispose to interstitial pneumonitis after marrow transplantation and is known to cause a hypersensitivity pneumonitis in other clinical settings. Cyclosporine has also been implicated in causing acute pulmonary edema, again from an initial insult to the capillary endothelium.[8] As can be seen, the milieu surrounding the marrow transplant is rife with

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ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
CMV = cytomegalovirus
UCSF = University of California, San Francisco

pulmonary toxins, and sorting out the specific culprits for pulmonary disease in an individual patient is often difficult.

What are the major causes of death after marrow transplantation, and how important are pulmonary complications in contributing to this death? Table 1 shows the major causes of death following transplant. About half of patients will suffer a pulmonary complication, and half of those will die of the complication.[3] Acute graft-versus-host disease, infection, and pulmonary complications (most notably pneumonia) are very much interrelated, and one cannot be implicated without the others being considered.

TABLE 1.—*Major Causes of Death in Patients Having Bone Marrow Transplants*

Cause of Death	Incidence (Percent)	Mortality (Percent)
Relapse of disease	20-60	80-100
Acute graft-versus-host disease	30-60	10-20
Infection (total)	2-3*	40-60
Pulmonary disease	40-60	50

*Episodes per patient.

TABLE 2.—*Early Pulmonary Complications of Marrow Transplantation*

Pulmonary Complication	Incidence, %
Infectious pneumonitis	40-60
Cytomegalovirus	
Bacterial	
Fungal	
Herpes simplex/varicella-zoster	
Protozoal	
Noninfectious pneumonitis	30-40
Idiopathic interstitial pneumonitis	
Transfusion reactions	
Mucositis	*
Cardiogenic pulmonary edema	*
Pleural effusions	16
Mechanical ventilation	21-26

*Incidence unknown.

Acute Graft-Versus-Host Disease

Acute graft-versus-host disease will develop in about half the patients between days 20 and 50 following allogeneic (non-twin sibling) marrow transplantation.[9] It is a clinicopathologic syndrome characterized by the triad of dermatitis, hepatitis, and enteritis. The common pathologic lesion involving these organs is the denuding of epithelium and lymphocytic infiltration. The severity of the acute disease is staged in each target organ and then graded based on the relative involvement of each site on a scale of 0 to 4. Grades 2 to 4, which represent moderate to life-threatening disease, are associated with an increased incidence of infection, interstitial pneumonia, and decreased survival. Although there are epithelial cells in the lung, there is no conclusive evidence that the lung is involved as a direct target organ in acute graft-versus-host disease. A report of an increase in the incidence of lymphocytic bronchitis as a specific manifestation of acute graft-versus-host disease has not been confirmed.[10]

Early Pulmonary Complications

Pulmonary complications of bone marrow transplantation are arbitrarily divided into early and late, based on the time after transplant. I will describe the early complications (Table 2) that occur between days 0 and 100, the most important of which is pneumonia.

The infectious pneumonias account for 40% to 60% of the early complications.[3] Of these, cytomegalovirus (CMV) interstitial pneumonitis is the most important because it both occurs frequently (40% to 50%) and carries a mortality of 70% to 90%. Cytomegalovirus pneumonitis alone accounts for as much as 20% of the total mortality after marrow transplant in some series.[11] Bacterial pneumonias are less common than CMV pneumonitis, probably because of the empiric use of broad-spectrum antibiotics during the neutropenic period. Fungal pneumonias, most notably *Candida* and *Aspergillus,* are also a major concern. They are less common than CMV interstitial pneumonitis and bacterial pneumonia in some series but are associated with a mortality rate of 70% to 90%.[3] Herpes simplex virus, although commonly activated after a marrow transplant, is uncommon as a cause of pneumonia, particularly without skin involvement.[12] Protozoal pneumonias, mainly due to *Pneumocystis carinii,* while once a common occurrence following a marrow transplant,

TABLE 3.—*Characteristics of UCSF Patients Having Bone Marrow Transplants*

Disease	Patients, No.	Type of Transplant: Allo(−)	Allo(+)	Auto	Risk: High	Good	Survived, No.
AML	23	5	0	18	10	13	14
ALL	5	3	2	0	5	0	2
CML	12	9	3	0	7	5	6
Hodgkin's disease	5	1	1	3	4	1	2
Non-Hodgkin's lymphoma	7	1	1	5	3	4	3
Multiple myeloma	2	1	0	1*	1	1	2
Aplastic anemia	2	2	0	0	1	1	2
Fanconi's anemia	1	1	0	0	1	0	0
Totals	57	23	7	27	32	25	31

ALL=acute lymphocytic leukemia, allo(−)=allogeneic matched transplant, allo(+)=allogeneic mismatched transplant, AML=acute myelogenous leukemia, auto=autologous transplant, CML=chronic myelogenous leukemia, UCSF=University of California, San Francisco

*This patient had a syngeneic transplant.

have been significantly reduced since the introduction of prophylaxis with the combination drug of trimethoprim and sulfamethoxazole.

Most noninfectious pneumonias are due to idiopathic interstitial pneumonitis, which accounts for 30% to 40% of early pneumonias.[13] As mentioned earlier, toxic agents have been implicated, and their relationship with idiopathic interstitial pneumonitis is unclear. Cardiogenic pulmonary edema should also be mentioned as a possible early complication. The incidence is not known, but multiple factors such as the intravenous administration of fluids, sepsis, and cardioactive drugs administered in the posttransplant period may interact to reduce myocardial contractility.

The incidence of pleural effusions following marrow transplant has not been previously reported; we found an incidence of 16%. Mechanical ventilation, although technically not a complication but a therapy for respiratory failure after marrow transplant, is included under early complications as an index of the severity of pulmonary complications. The largest series reported in the literature is from Seattle, where an incidence of 21% is described.[14]

The UCSF Experience

Table 3 shows the characteristics of the first 57 patients at UCSF undergoing a marrow transplantation. Of these 57 patients, 30 received allogeneic transplants and 27 autologous transplants where their marrow was previously harvested during a period of remission. Of the 30 allogeneic transplants, 23 were HLA-matched and nonreactive at the major histocompatibility complex, while 7 of the 30 were mismatched. Of the 57 patients, 32 were classified as high risk and 25 as good risk by standard criteria.[15] At 2½ years following transplant, 31 of the patients are still alive, for a survival of 54%. Of note, the high-risk patients carried a survival of less than 40%, while nearly 70% of the "good risk" patients survived. The risk factors for a decreased survival from our data are shown in Table 4. The factors that reached statistical significance were the risk status, histocompatibility, the use of total body irradiation or cyclophosphamide, and, most significantly, the development of pneumonia following transplant. It is well established from the literature that increasing age and the presence of graft-versus-host disease are risk factors for a decreased survival. We suspect that the failure of these factors to achieve significance is due to the relatively small number of patients who have thus far been transplanted in our program.

Mortality and cause of death are shown in Table 5. The leading cause of death in our patients was respiratory failure. Relapse of disease and sepsis combined did not contribute to mortality as heavily as respiratory failure. The pulmonary complications we observed are shown in Table 6. Pneumonia was the most common pulmonary complication, with an incidence of 35%. The leading cause of pneumonia was idiopathic interstitial pneumonia, which was defined by open-lung biopsy or postmortem examination. In all, 20% of pneumonias (four patients) were due to fungal infection, three having *Aspergillus* and one *Candida*. Pneumonia in two patients was classified as unknown; although culture data were negative in these patients, a tissue specimen was not examined. Only two patients (10% of those with pneumonia) had documented cytomegalovirus infection. Bacterial pneumonias were found in two and *P carinii* and *Mycobacterium tuberculosis* in one each.

Pneumonia following a marrow transplant often presents with bilateral interstitial infiltrates that may be diffuse in nature, and the chest radiograph is often not helpful in differentiating a cause. Pneumonia due to cytomegalovirus, fungal, or the interstitial variety is particularly difficult to differentiate. Some recent information suggests that if the process is initially focal rather than bilateral, *Aspergillus* pneumonia is the more likely diagnosis.[1]

Another pulmonary complication that we have seen is upper airway obstruction due to mucositis. Mucositis is common following marrow transplant due to the cytotoxic therapy, but it is uncommon for it to be so severe as to require endotracheal intubation as it did in one patient. Pleural effu-

TABLE 4.—*Risk Factors for Decreased Survival in UCSF Patients Having Bone Marrow Transplants*

Risk Factor	P *Value**
Risk, high versus good (standard)	<.02
Type of disease	NS
Age	NS
Allogeneic mismatch	<.02
Graft-versus-host disease	NS
Total body irradiation	<.02
Cyclophosphamide therapy	<.02
Pneumonia	<.01

NS=not significant, UCSF=University of California, San Francisco

*χ^2.

TABLE 5.—*Mortality in UCSF Patients Having Bone Marrow Transplants (n=57) and Cause of Death**

Cause of Death	*Patients, No. (%)*	*Autopsy, No.*
Respiratory failure	14 (54)	10
Relapse	5 (19)	0
Sepsis	3 (12)	2
Veno-occlusive disease	2 (8)	0
Cardiac failure (toxic)	1 (4)	0
Intracranial hemorrhage	1 (4)	0
Totals	26	12

UCSF=University of California, San Francisco

*Bone marrow transplants were done between January 16, 1986, and March 18, 1988; mortality figures are as of May 1, 1988.

TABLE 6.—*Pulmonary Complications in UCSF Patients Having Bone Marrow Transplants (n=57)*

Complication	*Patients, No. (%)*
Pneumonia*	19 (35)
Idiopathic	8 (14)
Fungal	4 (7)
Unknown	2 (4)
Cytomegalovirus	2 (4)
Bacterial	2 (4)
Pneumocystis carinii	1 (2)
Mycobacterial	1 (2)
Upper airway obstruction (mucositis)	1 (2)
Pleural effusion	9 (16)
Empyema	1 (2)
Mechanical ventilation	15 (26)

UCSF=University of California, San Francisco

*A total of 20 episodes occurred in 19 patients.

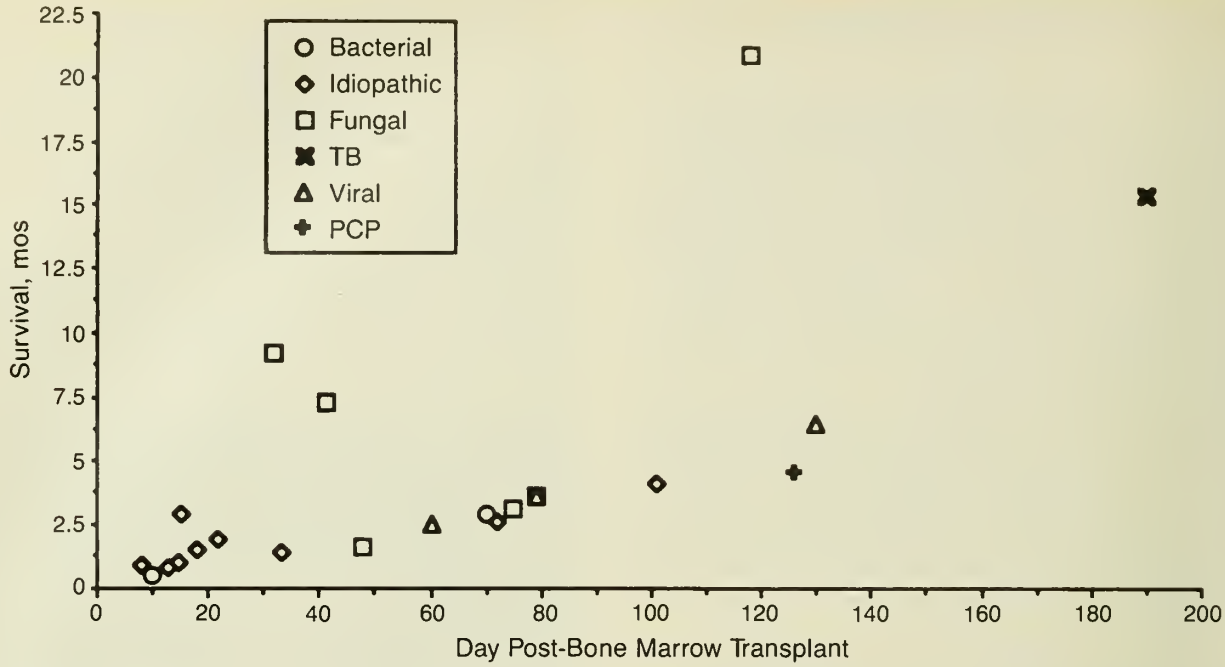

Figure 1.—The graph shows the timing of pneumonias after bone marrow transplants. PCP = *Pneumocystis carinii* pneumonia, TB = mycobacterial

sions occurred in nine (16%) of our patients. Of note, 39% of patients with nonbacterial, nonfungal pneumonia had pleural effusions. One of the effusions was an empyema caused by *Candida albicans* that required thoracostomy tube drainage. Mechanical ventilation was instituted in 15 (26%) patients, as will be discussed further.

Mortality from pneumonia in our patients was 74% (14 patients). The only patients who survived were those who had either a bacterial or an unknown cause. One of the patients with pneumonia of an unknown cause presented with bilateral interstitial infiltrates. Bronchoalveolar lavage was nondiagnostic, and no cause was determined, but the patient improved without specific therapy. The other patient with pneumonia of unknown cause temporally responded to empiric amphotericin B therapy.

The Timing of Pneumonia After Transplantation

The occurrence and type of pneumonia after a marrow transplant is related to the host defense status.[16] Initially a profound neutropenia results from the conditioning regimen. During this period, bacterial pneumonias are likely, and the most common organisms are coagulase-negative *Staphylococcus* and gram-negative organisms such as *Pseudomonas.* Patients are also predisposed to fungal pneumonia during this period. Herpes simplex infection also occurs during the first 20 days, probably due to reactivation from the stress of the transplant. If the graft takes, neutropenia usually resolves around the end of the third week. The major determinant of pneumonia then becomes the presence of graft-versus-host disease. Cytomegalovirus and idiopathic interstitial pneumonitis occur at about the same time, usually between days 30 and 75. Thus, during the first 30 days, CMV pneumonitis is unlikely, and bacterial and fungal pneumonias are more common. This sequence is helpful in determining a diagnostic strategy.[1]

Figure 1 shows the timing of pneumonia following marrow transplants in our patients. The cases of idiopathic interstitial pneumonia were clustered at or before day 30. In fact, the patient in whom idiopathic interstitial pneumonitis developed at day 100 was reinduced following relapse, and the pneumonitis occurred within day 30 of reinduction and could be added to the early group. This finding appears to be at odds with what is generally appreciated about idiopathic interstitial pneumonitis. Recent data from the Seattle group provide insight into this apparent discrepancy.[17] On review of 111 open-lung biopsy specimens in marrow transplant recipients with diffuse pulmonary infiltrates, the Seattle group has found that before day 30, only 5 of 26 revealed an infectious cause. Four of these five were fungal infections and the other bacterial. Furthermore, the idiopathic pneumonias fell into two groups: those that occurred before day 30 and were characterized clinically by alveolar hemorrhage and pathologically by alveolar hemorrhage and diffuse alveolar damage, and those that occurred after day 30 and pathologically were more consistent with interstitial pneumonitis and fibrosis. Our data are in agreement with these findings. The pathologic examination of lung tissue obtained by open-lung biopsy or at autopsy in those cases clustered before day 30 uniformly revealed alveolar hemorrhage with diffuse alveolar damage without viral inclusion bodies or culture evidence of infection. The patients in whom pneumonia occurred after day 30 showed interstitial mononuclear infiltration and fibrosis with honeycombing.

Risk Factors for Interstitial Pneumonitis

Some interesting information is obtained when the occurrence of interstitial pneumonitis is related to the type of transplant done. Marrow transplants are either autologous, allogeneic, or, rarely, syngeneic (identical twin). For idiopathic interstitial pneumonitis, the lowest incidence is observed with autologous transplants (4%), while an equal incidence occurs with allogeneic and syngeneic transplants (12%).[18] Because graft-versus-host disease does not occur in autologous or syngeneic transplants, it is unlikely to be an etiologic factor in idiopathic interstitial pneumonitis. When CMV pneumonitis is compared in the three groups, how-

ever, the highest incidence is found with allogeneic transplant (16%), whereas with autologous transplant the incidence is only 4%. Most interesting is the fact that CMV interstitial pneumonitis does not occur following a syngeneic transplant.[19] This is strong evidence linking graft-versus-host disease and CMV interstitial pneumonitis.

The risk factors for interstitial pneumonitis are shown in Table 7. Relevant factors are not only the type of transplant but also whether the transplant was done for a hematologic malignant disorder such as leukemia or for nonmalignancy—such as aplastic anemia—probably because transplant for nonmalignant lesions does not routinely entail the total body irradiation that is part of the conditioning regimen for malignant tumors. Total body irradiation is a risk factor for both CMV and idiopathic interstitial pneumonitis.[20] If the total body irradiation is administered in a single dose rather than in divided fractions, there seems to be an increased risk for idiopathic interstitial pneumonitis and possibly for CMV pneumonitis.[21] Methotrexate given as prophylaxis for graft-versus-host disease may also be a risk factor for idiopathic interstitial pneumonitis. Cytomegalovirus serologic tests are important in assessing the risk for subsequent CMV interstitial pneumonitis. Patients seropositive for CMV (depending on the area, the endemic rate may be 30% to 40%) before transplant have a higher incidence of CMV pneumonitis.[11] Seronegative patients who receive leukocyte transfusions are also at increased risk. All seronegative patients should receive seronegative blood products if possible.

Diagnosis of Diffuse Pulmonary Infiltrates After Transplantation

The diagnosis of diffuse pulmonary infiltrates that develop following a marrow transplant is one of the most challenging areas in managing bone marrow transplant patients and appears to be going through an evolution. The open-lung biopsy has long been considered the gold standard in evaluating diffuse infiltrates and yields a specific diagnosis in 60% to 70%,[22] but may contribute to death.[23] Transbronchial biopsy has a slightly lower yield of specific diagnoses and a comparable complication rate. Recent studies using high-volume bronchoalveolar lavage (BAL) in combination with new techniques in diagnosing viral infections suggest that yields approaching those of open-lung biopsy can be obtained with significantly less morbidity.[24-26] This is most pertinent when CMV is considered a likely culprit, for recent data challenge the necessity of open-lung biopsy to establish CMV as a cause.[26] The major deficiency of BAL appears to be in diagnosing fungal infections, particularly *Aspergillus.* The literature is lacking information on the sensitivity and specificity of BAL in diagnosing fungal infections, and, until more data are available, the open-lung biopsy remains the definitive procedure for diagnosing diffuse pulmonary infiltrates after marrow transplantation.[1]

Table 8 shows our experience with BAL in diffuse pulmonary infiltrates. A total of 15 lavages were done in 12 patients, and a definitive diagnosis was established in 2 instances. All lavage specimens were cultured for bacterial, fungal, and viral pathogens. In cases where the final pathologic diagnosis was idiopathic interstitial pneumonitis, BAL did not show any false-positive results for CMV. One lavage specimen was positive for herpes simplex virus in a patient with oral lesions, but subsequently the pathologic findings at autopsy did not support herpes simplex virus as the cause of the diffuse pulmonary infiltrates. A second patient with idiopathic interstitial pneumonitis on autopsy had respiratory syncytial virus antigen detected in a lavage specimen during what may have been a local epidemic. Respiratory syncytial virus was not recovered from the lung, and no viral inclusion bodies were detected at autopsy, thus this virus could not be established as the causal agent. Bronchoalveolar lavage established the diagnosis of CMV in one of two patients by culture. Currently the shell vial assay[27] is used as well as culture of BAL specimens for CMV, but this was not routine for most of the BAL data. Bronchoalveolar lavage was attempted in only one patient who was ultimately diagnosed as having *Aspergillus* infection. Lavage did not detect *Aspergillus* in that instance and should not be considered sufficient to exclude invasive aspergillosis if negative. For these data, the important point is that although a definitive diagnosis was not routinely established by BAL, therapy was not falsely directed. Current information from larger series suggests that by taking into account the prevalence of infectious causes in relation to the time after transplant and using appropriate viral diagnostic techniques, BAL may be sufficient to

TABLE 7.—*Risk Factors for Interstitial Pneumonitis*

- CMV Interstitial Pneumonitis
  - Type of transplant
  - Transplant for hematologic malignancy
  - Age (sharp increase after age 21)
  - Acute graft-versus-host disease (grade 2 or higher)
  - CMV seropositive before transplant
  - CMV-seronegative patients receiving leukocyte transfusions
  - Total body irradiation (single dose versus fractionated*)
- Idiopathic Interstitial Pneumonitis
  - Single-dose total body irradiation
  - Transplant for hematologic malignancy
  - Methotrexate prophylaxis for graft-versus-host disease in patients receiving total body irradiation*
  - Age*

CMV=cytomegalovirus

*Oata controversial.

TABLE 8.—*Bronchoalveolar Lavage (BAL) in the Diagnosis of Diffuse Pulmonary Infiltrates*

Type of Pneumonia	*BAL Findings*	*Pathologic Findings at Autopsy*
IIP	Nonspecific	Diffuse alveolar damage
IIP	Nonspecific	Diffuse alveolar damage
IIP (2)	Nonspecific; HSV (culture)	Diffuse alveolar damage; no evidence of HSV
IIP	Nonspecific	Diffuse alveolar damage and hemorrhage
IIP (2)	Nonspecific Nonspecific	Interstitial pneumonitis and fibrosis (both)
IIP	RSV (antigen)	Diffuse alveolar damage; no evidence of RSV
CMV	CMV (culture)	Viral inclusions (open-lung biopsy)
CMV	Nonspecific	Diffuse alveolar damage; viral inclusions
Aspergillus	Nonspecific	*Aspergillus*
Pneumocystis carinii	*P carinii* (Giemsa)	Not done
Unknown (2)	Nonspecific Nonspecific	Not done Not done
Unknown	Nonspecific	Not done

CMV=cytomegalovirus, HSV=herpes simplex virus, IIP=idiopathic interstitial pneumonitis, RSV=respiratory syncytial virus

diagnose or exclude most of the pathogens that produce diffuse pulmonary infiltrates. The glaring weakness is the unreliability of BAL to diagnose fungal infections, particularly *Aspergillus.*

Mechanical Ventilation

Information has recently become available about the incidence and outcome of bone marrow transplant patients who require mechanical ventilation for respiratory failure.[14] The Seattle experience described an incidence of 21%. Of 111 patients, 30 (27%) survived the initial episode, but only 6 (5%) were alive at six months. Three pretransplant risk factors were associated with a later need for ventilatory support: age older than 21 years, relapse of disease, and nonidentical HLA-matched donor and recipient. Survival after ventilatory support was not found to be associated with any pretransplant or posttransplant factors examined. Of the first 57 adult marrow transplants done at UCSF, 15 patients required mechanical ventilation, an incidence of 26%. All of the patients requiring mechanical ventilation for respiratory failure due to diffuse pulmonary infiltrates died. Two patients initially had their endotracheal tubes removed—including the patient with severe mucositis who required an endotracheal tube for airway protection—but both were subsequently reintubated within seven days and subsequently died. The mean duration of mechanical ventilation was 24 days. The reason for the worse outcome observed in our patients is unclear and likely reflects the small number of patients reviewed.

Pathogenesis of Interstitial Pneumonitis

Little is known about the pathogenic mechanisms involved in interstitial pneumonitis following marrow transplant. The pathologic findings in the idiopathic variety include diffuse alveolar damage with alveolar hemorrhage, which is nonspecific, and interstitial inflammation with fibrosis. Do these lesions represent a continuum? Does diffuse alveolar damage progress to interstitial pneumonitis and fibrosis? Are they two completely distinct disorders that deserve separate classification? How does the interplay of chemotherapy and irradiation relate to pathogenesis? Is there an undisclosed pathogen? Unfortunately, at this stage we have many more questions than answers.

More is known about the interstitial pneumonitis caused by cytomegalovirus. The relationship between CMV and graft-versus-host disease appears to be at the center of understanding the pathogenesis. Viral replication in and of itself is probably not enough to cause the severe tissue destruction observed. This is inferred from two clinical observations: the highest viral load occurs in CMV pneumonitis associated with the human immunodeficiency virus, yet tissue destruction does not compare with that following marrow transplant, and antiviral agents that stop replication have not been shown to abort the destructive process.[28,29] Fascinating recent data in a mouse model suggest that CMV can induce a graft-versus-host reaction and that both are required to produce interstitial pneumonitis, raising the possibility that CMV interstitial pneumonitis is an immunopathologic condition.[29]

Treatment and Prophylaxis of Interstitial Pneumonitis

The treatment of CMV pneumonitis has not met with much success,[30-32] and most efforts have been directed at defining regimens that may be beneficial as prophylaxis against infection. It is clear that using CMV-negative blood products in seronegative transplant recipients reduces the incidence of pneumonitis and improves survival.[33] The issue is controversial in seropositive patients. Acyclovir has not been shown to be effective in the treatment of CMV pneumonitis, but recent evidence suggests that when used prophylactically in high doses, the incidence of pneumonitis is reduced and survival is prolonged.[34] Ganciclovir, an antiviral agent with specific in vitro activity against CMV, while ineffective when used alone in treating pneumonitis, may be more effective as treatment when combined with CMV immune globulin. CMV immune globulin alone does not add to CMV-negative blood products in terms of prophylaxis and does not appear to influence survival when used alone as treatment of pneumonitis.[33,35] Clinical trials are underway to assess the role of foscarnet (phosphonoformate) in the treatment of CMV pneumonitis.[36]

While major advances have been made in prolonging the survival of marrow transplant recipients, pulmonary complications, most notably interstitial pneumonitis, represent the major challenge to further improving outcome, and efforts directed at better understanding its pathogenesis in order to tailor clinical trials are in progress.

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Epitomes

Important Advances in Clinical Medicine

Otolaryngology/Head and Neck Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology/head and neck surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in otolaryngology/head and neck surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology/Head and Neck Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Needle Aspiration of Peritonsillar Abscesses

PERITONSILLAR ABSCESS is the most common deep infection of the head and neck. It develops in the potential space between the tonsillar capsule and the superior constrictor muscle. Untreated, it can lead to more serious life-threatening deep-space infections of the retropharyngeal or pterygomaxillary space. In the past, standard recommended surgical therapy consisted of acute incision and drainage or acute abscess tonsillectomy. More recently, needle aspiration as the sole surgical intervention has proved to be effective in treating this disease.

The aspiration is carried out using an 18-gauge needle at a point about midway between the base of the uvula and upper alveolar ridge. A spinal needle may be used if trismus prevents the use of a standard 1½-inch needle. The abscess will resolve in about 90% of the patients with a single aspiration, with the other 10% resolving on one or two additional aspirations. Recovery from the disease is comparable to that of incision and drainage.

The advantages of this technique are its minimal morbidity, its cost-effectiveness, and its ease of performance. Although treatment of this process still remains within the purview of a head and neck specialist, generalists have been taught to do this procedure in geographic areas where an otolaryngologist may not be readily available. Culture and sensitivity of the aspirate yields *Peptostreptococcus,* group A streptococci, *Peptococcus,* and *Fusobacterium* in 75% of the cases. Penicillins or cephalosporins will provide adequate chemotherapeutic coverage in most cases. In two separate studies, however, culture results did not affect the outcome of the disease. Routine bacteriologic evaluation of the aspirate is then probably unnecessary and its elimination could contribute to additional cost-effectiveness. Admitting to hospital is unnecessary except when additional health considerations, such as altered immunity or dehydration, complicate the process.

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Scapular Osteocutaneous Free Flap for Mandibular Reconstruction

RECONSTRUCTING MANDIBULAR DEFECTS following trauma or cancer surgery has long been a challenging problem. While lateral defects may arguably be left unreconstructed or later undergo a staged reconstruction, defects of the anterior arch of the mandible cause such severe cosmetic and functional disabilities that immediate reconstruction is desirable. Preserving the normal facial profile and maintaining oral sphincter competence are of immense benefit to these patients.

Experience with nonvascularized bone grafts from ilium or rib has shown prohibitively high infection and graft loss rates when these grafts are placed in a field contaminated with saliva. They are more successful when used in a staged fashion where an entirely extraoral approach is possible. Using various metal reconstruction plates, frequently in conjunction with a pedicled myocutaneous flap, to bridge and stabilize anterior defects is another strategy. This approach, however, is also prone to problems related to infection, leading to plate exposure and extrusion, particularly in previously irradiated patients.

The scapular osteocutaneous flap is based on the circumflex scapular artery (a branch of the subscapular artery) and its accompanying veins. Direct perforators from fascia supply the skin, so the flap is thin and pliable. Because blood supply to skin and bone is separate, the bone graft and skin paddle can be positioned in a variety of complex three-dimensional relationships. Both skin and intraoral mucosa can be replaced simultaneously if portions of the flap are de-epithelialized.

The 6-cm vascular pedicle is of sufficient length to reach recipient vessels in the neck, and the vessel caliber is typically 2 mm, sufficient to ensure good patency rates. A 2- to 3-cm width of corticocancellous bone 12 to 14 cm long can be taken from the lateral border of the scapula. This is ade-

quate for defects reaching from one angle of the jaw to the opposite angle. Reattaching the teres muscles and active physical therapy postoperatively will minimize donor-site morbidity. One or two appropriately placed ostectomies allow contouring of the bone to the necessary curvature for anterior arch replacement. Small compression plates secure the bone graft in position.

Standard microvascular techniques of end-to-end or end-to-side anastomosis are used to reestablish perfusion to the flap. Although a microvascular flap transfer adds several hours to an already lengthy procedure, using a two-team approach allows the flap to be simultaneously harvested while primary tumor removal and neck dissection are done.

The two published clinical series using the scapular osteocutaneous flap for mandibular reconstruction report no flap failures and a 90% bony union rate in a total of 31 patients. Our own early clinical experience certainly supports this. The additional time and cost involved in doing a one-stage, vascularized reconstruction are justified when subsequent hospital admissions and surgical procedures can be obviated, delays in initiating planned combined radiotherapy can be avoided, and patients can have immediate restoration of appearance and function.

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Advances in Chemoprophylaxis for Head and Neck Surgical Wound Infections

PATIENTS UNDERGOING PROCEDURES of the head and neck are susceptible to wound infection because there is frequent contamination from bacterial flora of the upper aerodigestive tract. Studies have conclusively shown that using antibiotic prophylaxis substantially reduces this risk. More recent studies have provided further refinements in the guidelines for antibiotic prophylaxis in head and neck operations. Prolonged antibiotic administration, a commonly used practice, has no added benefit compared with short-term prophylaxis. It has now been clearly shown that the rate of wound infection for procedures that do not involve exposure of the aerodigestive tract—that is, clean wounds—is sufficiently low not to warrant routine antibiotic prophylaxis. Both of these observations represent substantial cost reductions. Risk factors that previously were thought to contribute to the development of wound infection, such as preoperative radiotherapy and chemotherapy, do not appear to be significant. Factors that carry the highest risk include the stage of the disease and the complexity of the operative procedure.

The choice of antibiotic that provides the best protection against wound infection remains controversial. Some studies support the use of broad-spectrum agents effective against most gram-positive aerobes including staphylococci and many gram-negative organisms. Other studies support the use of third-generation cephalosporins that are most effective against anaerobic organisms. These newer third-generation cephalosporins, however, are less effective against gram-positive and gram-negative aerobic organisms. A recent study indicated the etiologic importance of anaerobes in the development of head and neck wound infections. The combination of metronidazole, highly specific for anaerobes, and cefazolin was associated with a significantly lower infection rate when compared with prophylaxis with cefazolin alone (9.5% versus 18.6%). An added advantage of this combination is that newer antibiotics can be used therapeutically should wound infection develop.

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Moving Platform Posturography

EVALUATING DIZZINESS and balance disorders can be a complex challenge. The results of traditional neuro-otologic workups, which rely primarily on tests of the vestibulo-ocular reflex, are often negative in these patients. Because the somatosensory, visual, and vestibular systems all contribute to postural control in humans, Romberg test results are also often inconclusive. A new test of postural control, moving platform posturography, has been developed and is proving helpful in diagnosing and treating balance disorders.

Moving platform posturography tests a patient's ability to maintain balance in conditions with and without normal somatosensory and visual information for postural control. In addition to evaluating the patient's ability to use vestibular information to control posture, the test also assesses a patient's motor coordination, strength, quickness, and adaptability in the face of challenges to balance.

Extensive work has been done to establish normative data and patterns seen in diseased states. In one study of 80 patients with known peripheral vestibulopathies, 76 patients (95%) showed normal sway patterns in standard Romberg tests. Of the same group of patients, however, 77 (96%) had significant impairments in postural stability when normal somatosensory and visual cues for postural control were unavailable. Another study used moving platform posturography to study 74 patients aged 65 and older who complained of dizziness or imbalance. Almost all of these patients had signs of peripheral or central vestibulopathies, and 59 (80%) showed increased body sway in test conditions without normal visual and somatosensory cues for postural control.

In addition to providing information for diagnosis, this test can be used to evaluate the functional balance capacity of patients. Test results can be used to devise physical therapy programs or other rehabilitative procedures and to document recovery. For example, sequential tests in patients recovering from vestibular injury can graphically demonstrate the patients' ability or inability to compensate centrally for the injury. This information is valuable to both physicians and patients in assessing progress and directing the decision for further therapy.

In summary, moving platform posturography is rapidly becoming a useful adjunct to conventional neuro-otologic tests in evaluating dizziness and imbalance. In addition to

assessing a patient's ability to use vestibular information to control balance, this test provides a multifaceted assessment of motor responses to challenges to balance. It thus provides an important evaluation of a patient's functional balance capacity that can be used to direct rehabilitative programs.

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Improved Diagnosis of Acoustic Neuroma With Auditory Brain-Stem Evoked Responses and Gadolinium-Enhanced MRI

THE MOST FREQUENT REASON for a clinical suspicion of acoustic neuroma is a unilateral or asymmetric sensorineural hearing loss, although patients may present with persistent vertigo or other neurologic symptoms. As only about 5% of patients undergoing evaluation for an acoustic neuroma will ultimately be found to have a tumor, an efficient and economic diagnostic tree is essential. Following a standard audiometric evaluation, which identifies patients "at risk," auditory brain-stem evoked responses (ABRs) are obtained when there is sufficient residual high-frequency hearing. The ABR is a computer-averaged recording of the changes induced in the electroencephalogram due to sound stimulation. A series of peaks that correspond to different levels in the auditory central nervous system is generated. The results of the ABR are abnormal in more than 95% of patients with proven acoustic tumors. When the latency of the most prominent wave (V) is symmetric and within normal limits, an acoustic neuroma is improbable. The rare false-negative findings generally occur in patients whose acoustic tumors have arisen in the cerebellopontine angle, rather than within the internal auditory canal. False-positive ABR studies are common and indicate the need for an imaging study.

The definitive diagnosis of acoustic neuroma requires an anatomic visualization of the cerebellopontine angle and the internal auditory canal. Contrast-enhanced computed tomographic (CT) scanning reliably visualizes larger tumors but detects less than 50% of tumors that are less than 2 cm in diameter. As the ability to preserve the function of the auditory and facial nerves is highly dependent on tumor size, detecting tumors when they are small is a primary goal in acoustic tumor diagnosis. Recently magnetic resonance imaging (MRI) has become the diagnostic imaging technique of choice in the evaluation of acoustic neuromas, and it has numerous advantages over CT. It provides a noninvasive means of detecting very small tumors that previously would have required gas-contrast CT. False-negative studies appear to be exceedingly rare when a proper slice thickness and imaging technique are used. A few false-positive MRIs have been noted, especially in patients with large internal auditory canals. Within a wide canal that is partially compartmentalized by arachnoid webs, restricted cerebrospinal fluid circulation may lead to an increased protein concentration in the trapped fluid. This returns a bright signal on T2-weighted images. Until recently, adjudicating such equivocal MRI results required gas-contrast CT scans. The introduction of the MRI contrast agent, gadolinium DTPA, however, has rendered this unnecessary. This paramagnetic metal ion, which was recently approved by the Food and Drug Administration, induces a notable increase in the signal intensity of an acoustic neuroma. It has been used in more than 10,000 patients worldwide without significant morbidity. Aside from reducing the incidence of false-positive studies, gadolinium contrast MRI has, in our series, revealed several small tumors that were entirely inapparent on nonenhanced MRI scans. Gadolinium-enhanced MRI also appears to be useful in cases of possible recurrence where differentiating tumor from scar tissue or implanted muscle plug may be difficult using other techniques.

Magnetic resonance imaging also displays surgically important information that was not available on earlier studies. On MRI, the lateral extent of tumor penetration in the internal auditory canal can be evaluated. This both assists the surgeon in planning the operative route (translabyrinthine, retrosigmoid, or middle fossa) and in differentiating an acoustic neuroma from other cerebellopontine angle neoplasms such as meningiomas, which usually do not possess an intracanalicular component. Another advantage of MRI is its ability to visualize intrinsic brain-stem disease such as multiple sclerosis that may mimic the clinical presentation of an acoustic neuroma. In summary, MRI with gadolinium contrast has virtually rendered obsolete all other imaging methods used in diagnosing and characterizing acoustic neuroma. Computed tomography is reserved for those patients known to have metallic implants (MRI hazardous) and in those 5% to 10% of patients who, because of claustrophobia, are unable to tolerate insertion into the magnet.

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Implantable Hearing Aids

ONE OF THE NEW AND EXCITING ADVANCES in otolaryngology and head and neck surgery is the development of hearing devices designed to be implanted in the ear of patients with mixed or conductive hearing loss. These devices have some similarities to cochlear implants used for profound hearing loss, but the indications are different.

At this time two basic types exist. In one type a magnet-containing bone screw is inserted into the mastoid bone behind the ear. A modified hearing aid containing a microphone, amplifier, battery, and an output coil is worn externally with the coil lying over the implanted magnet. Sound amplified by the hearing aid goes to the coil, which energizes the magnet to vibrate the skull so that the patient hears by bone conduction. The ear canal is left open, avoiding problems of drainage and recurrent infection with a tight-fitting

ear mold. Sound quality is exceptionally good. This device appears to be an ideal solution for patients with bilateral canal atresia and inoperable conductive hearing loss.

In the other type, which is still in the experimental stage, a small magnet is placed in the middle ear on the stapes at the time of the middle ear operation. The vibrating element may be contained in a middle ear prosthesis and is externally energized using electromagnetic induction through an external hearing aid with coil. In this version the ossicles are directly vibrated rather than the mastoid bone, a much more efficient system. If the operation fails to totally correct the hearing loss, the implant component can be used to produce amplification. Again, the ear canal is open, minimizing the problems of a tight ear mold. In the simplest version, a magnet is encapsulated in a middle ear prosthesis so that it can be energized by an external coil to vibrate the ossicles. The sound is particularly clear and preferred compared with the sound of conventional hearing aids. Whereas this type of device is still experimental, it is expected to be available soon. The magnetic bone screw is available and is being used for the treatment of certain types of conductive and mixed hearing loss. In the future it may well be possible that these implant instruments will also be used for neurosensory loss because of the improved sound clarity they provide.

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Conserving Hearing in Acoustic Tumor Operations

OF THE 2,500 PATIENTS with acoustic tumors removed at the Otologic Medical Group, Los Angeles, only 5% were candidates for hearing preservation operations. Unfortunately, the tumor is usually too large at diagnosis for this procedure. In selected cases, however, hearing conservation may be possible using the middle fossa or retrosigmoid approach.

The two most important factors to be considered are the size of the tumor and the level of preoperative hearing. Secondary factors are the preoperative results of brain-stem evoked response audiometry (BERA) and electronystagmography (ENG).

The limit of the tumor size for the middle fossa approach is 1.5 cm and for the retrosigmoid approach is 1.5 to 2 cm. We also prefer patients with good preoperative hearing as candidates for hearing preservation operations. Our guidelines are a speech reception threshold of at least 30 dB and a speech discrimination of 70%.

In our series of 106 patients with removal of middle fossa acoustic tumors, patients with tumors arising from the superior vestibular nerve had a better hearing outcome than those with tumors from the inferior vestibular nerve. This may reflect a greater involvement of the cochlear nerve or cochlear blood supply by tumors developing in the inferior compartment of the internal auditory canal. Preoperative ENG is helpful to predict tumor origin. When such testing showed hypoactive calorics, indicating a superior vestibular nerve tumor, hearing was preserved in 64% of patients. Only 48% of patients had their hearing preserved when the preoperative calorics were normal.

There is a trend toward a better rate of hearing preservation with a relatively normal preoperative results of BERA. For patients with a preoperative intra-aural wave V latency difference of 0.4 milliseconds or less, hearing was preserved in 78%. For greater latency differences, the hearing preservation rate dropped to 58%. With no response on BERA, postoperative measurable hearing remained in only 50% of patients.

In summary, the ideal candidate for hearing preservation during acoustic tumor removal should have good preoperative hearing, a small tumor, near-normal preoperative results on BERA, and hypoactive calorics on preoperative ENG. The needs of the patient should also be considered, however, and these criteria should be tailored to each patient.

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Botulinum Toxin for Treatment of Spastic Dysphonia

SPASTIC DYSPHONIA is a voice disorder of unclear etiology yet clinically distinguishable by strained, staccato, effortful speech with voice arrests. The vocal abnormality results from spasm or hyperadduction of true and false vocal cords. It is believed to be a focal dystonia, similar to essential blepharospasm, yet the underlying pathophysiology is poorly understood. It has been proposed to be a heterogeneous disorder including different subtypes—psychogenic, neurologic, and idiopathic—or part of a generalized neurologic disorder.

Diagnosing spastic dysphonia involves subjectively evaluating a patient's speech. Although videostroboscopy can be helpful in identifying a laryngeal tremor, standard laryngoscopy, acoustic analysis, glottography, and electromyography are often not helpful. A lack of understanding of the pathophysiology of this disorder has resulted in a myriad of treatments including speech therapy, psychotherapy, biofeedback, muscle relaxants, tranquilizers, and anticonvulsant therapy. The results from these types of therapy, however, have been disappointing. In 1976 recurrent laryngeal nerve section was introduced, which has been the single most effective treatment of refractory spastic dysphonia. The initial results were excellent, but recent long-term reports have found the results to be temporary with a return of symptoms despite unilateral vocal cord paralysis.

Botulinum toxin has been used to temporarily paralyze selected muscle groups to relieve spasm in such conditions as blepharospasm, torticollis, and, more recently, spastic dysphonia. Botulinum toxin A is one of the neurotoxins produced by *Clostridium botulinum.* It interferes with presyn-

aptic release of acetylcholine from the nerve ending, thereby functionally denervating muscle fibers for weeks to months. Chemical denervation of the vocalis-thyroarytenoid muscle is accomplished by percutaneous localization of the muscle using a hollow electromyographic electrode followed by the administration of a small amount (0.1 to 0.3 ml) of toxin. Initially patients may experience hoarseness and aspiration that subsides in 36 to 48 hours, and increased fluency ensues. Vocal fluency should continue for three to six months, after which the injections can be repeated. In contrast to surgical treatment, both vocal cords can safely be treated eliminating failure due to the functioning cord. Although systemic effects appear subclinical at the present dosage, the long-term effects of the toxin in the larynx are unknown. Studies show that many patients feel the effect of the toxin to be preferable to other pharmacologic therapy. Most patients return for reinjection before their symptoms return. Further study is necessary, but it appears that botulinum toxin is an important new treatment option for patients with debilitating spastic dysphonia.

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Craniofacial Resection for Cancer

IN THE PAST, patients with advanced paranasal sinus neoplasms involving the anterior skull base had a dismal prognosis, and the lesions were generally considered unresectable. In the 1950s, extensive procedures were developed to remove these tumors, yet the outcome of surgical treatment was nearly as bleak as from the tumor, with most patients suffering significant morbidity. Now there is new hope for these patients with the current methods of surgical resection.

There are several reasons for the increased acceptance and success of craniofacial resection. Previously unresectable lesions are now surgically approachable, thanks to new technology and improved surgical techniques. With the progress of computed tomography and magnetic resonance imaging, lesions may be diagnosed while they are smaller and more resectable. Precise anatomic localization has permitted a better selection of surgical candidates and more detailed preoperative planning. Perioperative morbidity and mortality have been substantially decreased to acceptable levels (10% to 15% and less than 5%, respectively) with recent advances in intraoperative and postoperative monitoring techniques. Innovations in reconstructive techniques have allowed improved rehabilitation and reduced the risk of cerebrospinal fluid leaks and other complications. It is important for practitioners to be aware that such a procedure is now available to counsel patients appropriately.

Indications for craniofacial resection include malignant tumors arising from the nasal cavity, maxillary antrum, ethmoid-sphenoid complex, or orbit and extending to or through the cribriform plate. Investigators have found that even patients with some intracranial invasion often do well with this operation. Most candidates for craniofacial resection have already failed other forms of therapy, such as more limited surgical procedures or irradiation or both. Tumor types most commonly include squamous carcinoma, adenocarcinoma, esthesioneuroblastoma (olfactory neuroblastoma), and sarcoma. The best local control is achieved in well-differentiated squamous carcinoma and adenocarcinomas.

In this surgical approach, wide access is gained to the complex structures of the anterior skull base by a coronal flap and frontal craniotomy in combination with a facial incision. The cribriform plate and adjacent dura are removed en bloc with the ethmoid sinuses, nasal contents, and other involved structures such as the orbit or maxilla. The dura is repaired with fascia, the floor of the cranial fossa is reconstructed with a pericranial flap, and the nasal portion of the defect is lined with a skin graft. The cosmetic result is excellent. This is an oncologically sound en bloc procedure, and several series have now shown at least a three- to five-year disease-free survival in about half of these previously "incurable" patients.

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Intraoperative Facial and Auditory Nerve Monitoring

THE GENERAL PRINCIPLES underlying intraoperative monitoring of patients have been well established in anesthesiology: to provide an ongoing record of some physiologic function, to alert the surgeon when an undesirable change in that function occurs, and to provide feedback as to the efficacy of corrective measures that were taken. Through the development of specialized electrophysiologic monitoring techniques, preserving auditory and facial nerve function during surgical treatment in the posterior cranial fossa is becoming more the standard than the hoped-for exception of previous years. Moreover, these goals can be achieved noninvasively and without significantly delaying the operation.

Monitoring of the facial nerve is useful in the following: identifying surgical trauma to the nerve early, enabling the immediate notification of the surgeon; distinguishing facial nerve from adjacent nerves or from surrounding tissue or tumor; facilitating tumor removal by electrically mapping regions of the tumor for the presence of facial nerve; confirming nerve stimulatability following tumor removal in order to predict postoperative facial nerve function; and identifying the site and degree of neural degeneration in patients explored for possible facial nerve neoplasm or decompression of acute facial paralysis. Monitoring of facial function is carried out using standard electromyographic recording techniques with needle electrodes placed in the periorbital and perioral musculature. Facial nerve activity following stimulation, either unintentional as the result of trauma, or intentional using a hand-held stimulator, is monitored visually on a screen or routed to an audio amplifier for immediate feedback to the surgeon. The predictive efficiency for facial nerve function a year after the operation has been reported to be as high as 88%.

Monitoring auditory nerve integrity is accomplished using standard techniques for evoking the auditory brain-

stem response, during surgical treatment of the posterior fossa such as acoustic tumor removal, vestibular nerve sections, microvascular decompressions of adjacent cranial nerves, and removal of other vascular or neoplastic lesions in proximity to the auditory nerve. As with other forms of monitoring, its value lies in providing immediate notification of significant changes in response amplitude and latency associated with surgical manipulation of the nerve or brain stem. Such changes, if uncorrected, may precede complete degeneration of the response, leading to profound, irreversible hearing loss postoperatively. If the response remains stable throughout the operation, the postoperative auditory status will be essentially unchanged from preoperative. Postoperative worsening of hearing is predicted with approximately 80% efficiency when persistent latency delays occur. Intraoperative monitoring of auditory brain-stem evoked responses provides the most direct means of assuring the preservation of auditory function during posterior fossa procedures.

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Editorials

A Nation's Health in Jeopardy

A NATION'S HEALTH has many facets, some of which at first may not seem to be related to health, in the common use of the word. But the meaning of health has come to be far more than simply the absence of illness. In fact, people often say they are healthy even when they know they have some disease or impairment. In a larger sense health is coming to mean more a state of being well or being in satisfactory adjustment to the stresses of one's internal and external environment. In like fashion, a nation's health may be thought of in terms of its adjustment to its own internal and external stresses, and it goes without saying that a healthy nation must have its foundation in a healthy citizenry. The health of its citizens affects the health and strength of a nation, and the converse is also true.

If one thinks of the health of a nation in terms of its physical, social, economic, and political health, one can begin to sense some strengths and some weaknesses. Physical health would include the health of the population and the health of the physical environment in which its citizens must live. Social health might include such things as literacy, education, social adjustment, and healthy life-styles and behaviors. Economic health can be thought of in terms of adequate productivity and provident use of economic resources, especially when some of the resources are in short supply. Political health might mean a stable government that promotes health in its broadest sense, attends to the freedom, safety, and well being of its citizens, and is responsive to their individual and collective needs and aspirations.

For some time this nation has led the world in achieving success in many of these measures of national health. More recently, there is reason to think that many stresses in both the internal and external national environment have been increasing faster than has our adjustment to them. To the extent that this imbalance has occurred our national health is in jeopardy. Some of the data are disturbing. Infant mortality rates have begun to rise for the first time in years. The elderly receive excellent health care on the whole, while many disadvantaged youth do not. There are millions in and out of the work force who do not have any health insurance at all and, therefore, less access to health care. There are unsolved problems of pollution of land, water, and air. The education of our youth is falling behind that in other nations with whom we must compete in a shrinking world with limited resources. There are the homeless in seemingly increasing numbers, and there are pervasive life-styles that result in widespread personal ill health. Our economy is under severe stress both internally to meet domestic needs and externally to meet unprecedented economic competition. Our political system has worked better than most, but its actions have done little to allow us to face up to a future that is already upon us. Political vision, resolve, and action seem too often limited by what needs to be done to win the next election.

Health, whether of a person, a population, an environment, a society, an economy, or even a body politic, is a long-term affair. We do not seem to be prepared to deal with this either in the public sector of government, where the time frame points toward winning the next election, or in the private sector, where the focus is on the bottom line or the reality of the next stockholders' meeting. If such as this is the case, it seems evident enough that the health of the nation, using the criteria we have given, is in jeopardy. Realistically, it is too much to expect that the needed leadership will come from either government or the private sector of business and industry. It must come from somewhere else—a potent third force must be created.

Perhaps there is something of a model for this third force. The environmental movement might be an example. It has developed and grown outside both government and business and industry, yet it has had a considerable effect on both. Its interests have been largely devoted to preserving the natural environment wherever it has been threatened. But more recently the environmental movement has become more concerned with pollution of the air, water, and land. This brings its activities within the broad dimensions of health. Could this movement be some kind of a model for a needed third force to stimulate and coordinate the continuing effort that will be needed if ours is to be the healthy nation that it can and should be? Issues of health, if we accept their broader dimensions, pervade every aspect of national life. They affect the health of every citizen and the health of the nation itself. It would need a collaborative effort of many interests that share the common goal to make this a healthy nation in the fullest sense of the word. Can something like this happen? Will it happen? It really must happen, if there is to be a better future for our nation and our children.

MSMW

Cocaine and Pregnancy—Implications for the Child

IN THE PAST FEW YEARS, problems associated with drug use in pregnancy have become endemic. As cocaine has become the drug of choice for millions of Americans, including pregnant women, as AIDS has become more commonly recognized in women and infants, and as legal cases have begun to raise the question of fetal abuse, physicians, nurses, social service agencies, and public health officials have all been faced with an increasing number of infants showing the detrimental effects of their mothers' drug use.

Although problems of substance abuse in pregnancy have received increasing attention in the medical literature since the early 1970s, there has recently been a rapid increase in the number of articles published related to this field. The reasons for this new interest are easily understood when current statistics from the National Institute on Drug Abuse are reviewed.[1] Although patterns of abuse of alcohol, marijuana, heroin, and other substances by women of childbearing age have changed very little over the past ten years, the incidence of cocaine use in this special population has been rising rapidly, a reflection of cocaine's increasing popularity among the general population of the United States.

Additionally, our concept of teratology has changed in that we now recognize that, although most drugs of use and abuse do not produce congenital malformations, there are definite behavioral and neurologic effects that place the neonate, infant, and child at risk for developmental abnormality.

Early studies evaluating drug use by women during pregnancy revealed that around 50% to 60% of women used some analgesics during pregnancy and sedative drug use by preg-

nant women ranged around 25%.[2] Most women involved in studies such as these were receiving prenatal care and obtaining many of the medications by prescription from their physicians. The use of illicit drugs was rarely considered. During a six-month period in 1982, screening of all women enrolling at Prentice Women's Hospital and Maternity Center/Northwestern Memorial Hospital in Chicago for routine prenatal care showed that 3% of these women had sedative-hypnotics in their urine at the time of admission to the general maternity clinic.[3] This study was performed before cocaine became society's drug of choice. The incidence of cocaine use in pregnancy ranges from 5% of all deliveries at Northwestern Memorial Hospital to 17% of all pregnant women receiving prenatal care in a Boston City Hospital study (B. Zuckerman, MD, Associate Professor of Pediatrics, oral communication, April 1988). These figures are only an early indication of the widespread nature of the problem.

Unfortunately, the risk maternal drug use poses for the child does not end at birth. In New York City, it was estimated that 50% of all child abuse and neglect cases involved drug abuse, and if alcohol was included, substance abuse was involved in 64% of child abuse cases (M. Marriott, "Child Abuse Cases Swamping New York City's Family Court," *New York Times,* November 15, 1987, p 17). In a survey conducted by the Child Abuse Prevention Program, Department of Health Services in Los Angeles, of 5,973 cases of child abuse reported in 1985, a total of 538 cases (9%) involved neonatal withdrawal due to maternal drug use in pregnancy. In the first six months of 1986, 403 of 4,299 cases (9.4%) of child abuse were reported due to maternal addiction during pregnancy. The patterns of drug use in this population showed a shift toward a higher frequency of cocaine use among the reported cases in the first six months of 1986 as compared to 1985.

In Illinois in fiscal year 1987, more than 91,000 infants and children were reported to the state child abuse hotline, a 50% increase over fiscal year 1986. Of those reports, 530 were due to the finding of a drug of abuse in a neonate's urine. This represented a 77% increase in such reports over a year's span. Even so, the majority of cases of maternal substance abuse in pregnancy go undetected and unreported.

A study conducted in 1986 by the Illinois Department of Children and Family Services (DCFS) evaluated a random sample of 385 children who had become wards of the state due to abuse or neglect and who subsequently had been placed in foster care. It was found that about half of these children came from parents or caretakers who were known or suspected substance abusers. These parents were often reluctant to accept help: 55% rejected social services when offered, and 68% rejected substance abuse services. In addition, and perhaps most striking, 11% of these children in foster care had had serious medical problems (abstinence, seizures, respiratory distress) at birth related to in utero exposure to substances of abuse.

With the current shift to cocaine as one of the most common primary drugs of abuse, polydrug abuse has also become more common, with the majority of cocaine users abusing marijuana, alcohol, or cigarettes in addition. Thus, an evaluation of risk factors for a pregnant substance abuser and her newborn must take into consideration the effects of these secondary drugs of abuse. Another mediating factor in a fetus's response to drug exposure is the ability to metabolize and tolerate the illicit drug. This ability is determined through a variety of genetic and physiologic factors.

Many other factors in the environment of a pregnant substance-abusing woman, including poor nutrition, lack of prenatal care, maternal psychopathology, and the drug-seeking life-style, affect the ultimate outcome of a passively exposed infant and must be considered in interpreting clinical and research information.

Little reliable information regarding the long-term outcome of infants with passive exposure to drugs of abuse is available. To best evaluate these children at school age, environmental factors must be taken into account. These environmental factors are not only socioeconomic but should encompass aspects of the maternal-infant relationship, including maternal psychopathology and personality. One study that attempted to control for the caretaking environment of substance-exposed children compared these infants with those whose families began to use drugs after the birth of the children.[4] No differences were found between the in utero-exposed children and the children exposed to the social environment of drug-using caretakers. Further studies are needed before final conclusions can be drawn as to the long-term effects of in utero drug exposure on infant and child development.

The problems involved in evaluating the effects of maternal exposure to substances of abuse on the developing fetus and infant are multiple, not the least of which are the difficulties involved in following these infants over a long period of time. The chaotic and transient nature of the drug-seeking environment impairs the intensive follow-up and early intervention processes necessary to ensure maximum development by each infant. In addition, most women from substance-abusing backgrounds lack a proper model for parenting. These factors, compounded by the early neurobehavioral deficits of drug-exposed newborns, earmark these infants to be at high risk for continuing developmental and later school problems.

A key problem in the field of substance abuse in pregnancy is a public and professional lack of knowledge of the subject. Few prospective parents recognize that their life-style, especially drug use and abuse, has a powerful effect on the outcome of their newborn infant. Information about the hazards of substance abuse during pregnancy must be presented to the public in a straightforward, nonjudgmental manner. In this way, information regarding the effects of any licit or illicit drug use during pregnancy can become part of the public consciousness.

It is easy to overlook a newborn's passive exposure to drugs of abuse, for the assessment of maternal chemical dependence tends to be insufficient in most instances. Currently, pediatricians often must rely on scanty information from the prenatal period when assessing a newborn displaying withdrawal or the neurotoxic effects of drug exposure. A study of alcoholism by Sokol and colleagues found that "clinicians are continuing to miss the diagnosis in at least three of every four alcohol-abusing patients. It is unlikely that there is any other obstetric diagnosis that is missed as often."[5] Few patients today limit their abuse to alcohol and, with the current phenomenon of polydrug abuse, chemical dependence in pregnant women with the concomitant effects in newborns most assuredly is one of the most frequently missed diagnoses in the perinatal period. When an untoward event in the perinatal period does occur, whether it be a

perinatal cerebral infarction, unexpected premature delivery or an unexplained accident of pregnancy such as an abruption, maternal substance abuse must be placed in the differential diagnosis. An irritable newborn or one with unusual complications should be assessed with a full historical evaluation for substance exposure and, when indicated, a full toxicologic urine screen. Pediatricians have come to realize that intrauterine drug exposure has become a major cause of perinatal morbidity and mortality and an area that can no longer be overlooked.[6]

The developmental risks imposed by the maternal use of substances of abuse are, perhaps more than many other risk factors, preventable. The first step in prevention and intervention, however, relies on the establishment in the medical and public sectors of a perception of risk. This perception should be based on education of the public as to the clear effects maternal substance abuse has on pregnancy and neonatal outcome. Second, the medical and psychological communities must begin to better understand risk-taking behavior and the personality and motivational factors that engender and enhance this behavior. We must delineate the measurable outcomes that best express the damage of maternal substance abuse to the child, then use the most effective means of increasing the public's recognition of this risk and influencing the individual's will to act to reduce relevant risk-taking behavior.

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Myocarditis and Dilated Cardiomyopathy

ACUTE MYOCARDITIS is a clinical diagnosis that can be made with confidence when a previously healthy child or young adult has a new onset of abnormal cardiac function—as reflected in left or right (or both) ventricular failure, serious ventricular arrhythmia, or conduction disturbance—in the setting of an acute febrile illness specifically associated with a known microorganism such as measles, infectious mononucleosis, mycoplasma infection, trypanosomiasis[1] and in the absence of cardiodepressant drugs, toxins, or other systemic disease. As a rule, because of the generally benign course—often even subclinical—such cases rarely come to the attention of an internist or cardiologist. The diagnosis of myocarditis is facilitated by the presence of tachycardia out of proportion to fever and systemic illness, by evidence of pericarditis, by myositis, and by epidemiologic evidence of exposure to cardiotropic microorganisms. Notwithstanding the availability of rather safe methods of obtaining myocardial tissue for histopathologic study, relatively few patients have undergone myocardial biopsy in this acute setting. In young age groups, the exclusion of other forms of heart disease by other than general clinical means is hardly necessary, whereas in older persons the possibility of silent coronary artery disease or preexistent chronic subclinical cardiomyopathy must always be considered.

While the majority of such patients survive and go on to full clinical recovery, a significant number of patients observed carefully have shown clinical evidence of a chronic cardiomyopathy.[2,3] In one subset, ongoing myocardial inflammatory lesions found by myocardial biopsy on autopsy justify the diagnosis of subacute or chronic myocarditis,[4] whereas another subset of patients manifests dilated cardiomyopathy without histologic evidence of active myocarditis.[5]

This wide spectrum of the natural course of acute infection involving the myocardium mandates close follow-up of all patients with acute myocarditis for late stable or progressive myocardial dysfunction, which may for a long time remain subclinical. When present, however, this disorder should dictate appropriate therapy and especially secondary prevention by control of preload and afterload—including restriction of activity in some cases—and by protection of the person from cardiotoxins such as ethanol.

It is, however, another group of patients who come to the attention of internists and cardiologists with considerably greater frequency, namely, patients who have experienced a relatively recent onset of congestive heart failure without a history of acute myocarditis and who, in the absence of evidence of congenital, valvular, coronary artery, or specific heart muscle disease, are diagnosed as having dilated cardiomyopathy. An endomyocardial biopsy is frequently carried out in this patient group and, depending on the population sampled, the number of specimens taken, and the pathologic criteria used, a significant percentage are diagnosed as having active myocarditis. It is this type of patient that is discussed elsewhere in this issue. O'Connell and Mason present a comprehensive review of both clinical and experimental evidence for the infectious-immune cause of chronic, dilated cardiomyopathy. According to this concept, whereas the initial myocardial disease is directly related to the infectious agent, usually a virus, the ensuing progressive myocardial damage and fibrosis, with or without persistent inflammation, is attributable to immune or autoimmune processes. One may wonder why, in view of the multifaceted evidence presented, the infectious-immune cause of some cases of dilated cardiomyopathy continues to be labeled as a hypothesis for which evidence remains circumstantial.

In individual inbred strains of mice, the myocardial response to acute experimental infection with a specific strain of a specific virus tends to be remarkably uniform, but there is a wide variation of expression of the response in different strains.[6,7] Thus, it is entirely unreasonable to expect a uniform response to acute viral infections in humans, an outbred species, exposed to many different viruses and even strains of viruses. We are not surprised, then, at the wide spectrum of clinical expression seen in acute outbreaks of viral disease. A similar wide spectrum of myocardial involvement has recently been observed in an outbred animal—the pig—exposed to a myotropic strain of encephalomyocarditis virus.[8] In this connection, the reports of familial myocarditis quoted by O'Connell and Mason are also relevant.

With regard to the diagnosis of myocarditis, we may be disadvantaged by the definition of myocarditis as an inflam-

matory reaction of the myocardium, a definition reemphasized by the criteria developed by Aretz and colleagues, which base the diagnosis on the histopathologic demonstration of coexisting myocyte necrosis and cellular infiltration.[9] Without denying the clinical value if not necessity of diagnostic standards such as the Dallas criteria, we wonder if our understanding of the biology of the cardiac effects of viral infections and associated immune or autoimmune reactions may not be better served by keeping an open mind with regard to the morphologic and functional expressions of viral and immunologic effects on the heart. Viruses may also invade interstitial cells such as fibroblasts, as well as vascular smooth muscle cells. The effects of such involvement on cardiac function have hardly been explored, although recently the cytoskeleton has been given some attention in the pathogenesis of dilated cardiomyopathy.[10]

Such concepts might lead to surveys of patients with acute viral disease by means of radionuclide studies such as antimyosin scans,[11] along with noninvasive assessments of cardiac function such as echocardiograms and radioventriculograms, and with endomyocardial biopsies, with follow-up to determine the incidence of later evidence for dilated cardiomyopathy.

As a logical result of the increasing evidence for a role of the immune system in ongoing subacute and chronic myocardial inflammatory processes, immunosuppressive therapy has come into increasing clinical use, not only in patients with biopsy results positive for active myocarditis, but also in patients with dilated cardiomyopathy of recent onset. In view of the absence of proof of the effectiveness and the significant side effects of immunosuppressive agents, the controlled randomized trial described by O'Connell and Mason is of the utmost importance. The considerable differences in immunologic processes found in different strains of inbred mice,[6,7] however, suggest that immunosuppressive therapy with one agent may not be uniformly effective. It is hoped that the simultaneous study of indices of humoral and cellular immunopathogenetic factors will permit an analysis of the effect of immunosuppressive therapy in relation to subgroups of patients. It would be erroneous, however, to conclude that the immune system has only a deleterious effect on the myocardium in this disease. Studies of experimental viral infection in mice have shown that suppression of the immune system during the viremic phase of the infection may enhance myocardial replication of virus and myocardial damage.[12,13] Thus, immunosuppressive therapy should not be considered during the acute viremic phase of a viral myocarditis.

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The Fetus as Patient

A GENERATION AGO the human fetus seemed a mystery, hidden within the walls of the uterus and far removed from the efforts of diagnostic and therapeutic medicine. This began to change in a significant way with the advent of amniocentesis in cases of Rh isoimmunization in the 1950s, followed by genetic amniocentesis in the 1960s to determine the fetal chromosomal status. By the 1970s, sonographic imaging of the fetus had matured to the point of providing detailed and clinically useful anatomic information within the womb. It could truly be said that the walls separating the physician from the fetus had crumbled and that during pregnancy there now were two patients calling on the skill and technology of modern medicine, the mother and her unborn baby.

The rapid progress in fetal medicine has been exciting to its practitioners and to most families who seek medical information about their unborn babies. As of the present, diagnostic efforts have greatly outstripped therapeutic ones on behalf of the fetus, however. This situation is not unexpected and parallels most other new areas in medicine. A future era of expanded fetal therapeutic options will stand rightfully on an established understanding of normal fetal development and physiology and the refined ability to make correct diagnoses.

A concomitant of rapid progress is a certain level of confusion in other areas of society, including the law, as to the meaning and implications of fetal medicine. Debates have sprung up about the existence and extent of a fetal right to medical intervention, about possible expected behaviors of a mother vis-à-vis her fetus, and about the means of resolution or adjudication if there seems to be a conflict between maternal (or paternal) and fetal interests. Controversy about elective abortion greatly complicates these questions. It is likely that we will have continued unrest surrounding these issues for quite some time.

The success of prenatal diagnosis has coincided with the willingness to go to the fetus—that is, to enter the womb for diagnostic testing. From the point of view of risks and complications to the fetus and pregnancy, it would be preferable to stay outside of the womb and make do with maternal blood and urine specimens, abdominal palpation and auscultation, or other innocuous examinations. With the exception of measurements of maternal serum α-fetoprotein concentrations, this safest approach has not yet been fruitful for the diagnosis of fetal disease. Even so, it is axiomatic that the least invasive modality of fetal examination be chosen consistent with being able to accomplish a desired diagnosis.

One can draw obvious parallels in the diagnostic ap-

proaches to the postnatal versus the prenatal patient. For imaging after birth we use our eyes, x-ray films, magnetic resonance, and sound waves. For imaging the fetus, sonography is the mainstay; it gives excellent definition of both surface and internal anatomy as well as certain behaviors or functions of the fetus such as urination, breathing, blood flow, and heart action. Magnetic resonance imaging of the fetus is in its infancy and transabdominal endoscopic (fetoscopic) visualization has limited use because of relatively high risks. Sonography, on the other hand, has thus far proved risk free. With continually improving quality, sonographic imaging has become indispensable for visualizing the fetus and, equally important, for guiding intrauterine tissue sampling and therapeutic efforts.

Blood and urine analyses are crucial diagnostic tests postnatally. Amniotic fluid substitutes to some extent for urine in utero because fetal urine is a major constituent in the second and third trimesters. The appearance of metabolic products in amniotic fluid is attenuated, however, because of the continuous dialysis that occurs in the placenta. Blood sampling from the umbilical cord provides small but adequate specimens for the measurement of plasma constituents and the study of cellular components. Access to the fetal blood stream has become important not only for diagnosis but also for initiating and observing therapeutic interventions. Intrauterine umbilical vein transfusions for severe anemia in the fetus are increasingly being guided by concurrent measurements of the fetal hematocrit.[1]

Tissue or cellular biopsy is another conspicuous modality for diagnosis in the postnatal patient. It, too, has its parallel in utero. In fact, except for anatomic definition by ultrasonography, cellular analyses have been the most often used diagnostic studies of the fetus. The emphasis on genetic definition of the fetus has called for chromosomal, DNA, and enzyme analyses and these, in turn, have required cells. Within the womb, however, there have been two convenient sources of cells apart from the fetal body proper. These are the cells suspended in amniotic fluid, obtained by amniocentesis, and cells from the placenta, obtained by chorionic villus biopsy. Cells from both sites contain the fetal genome and in most respects accurately reflect the fetal genetic status. Amniocentesis in the second trimester has been used widely for two decades with a small risk of miscarriage, estimated at 0.5% to 1% or less.[2,3] Chorionic villus sampling in the first trimester is the subject of current investigations; its attendant fetal loss rate appears to be only slightly higher, less than 1%, than that of amniocentesis.[4]

Fetal tissue sampling directly from the fetal body is also done. Blood sampling is the most important technique and gives access to erythrocytes, leukocytes, and platelets. Skin biopsy and liver biopsy have also been developed but are used infrequently because diagnostic questions rarely require those tissues and the risks of the procedures remain relatively high.

Golbus and co-workers elsewhere in this issue report their long experience with fetal tissue sampling. The major experience is with fetal blood sampling, and they chronicle the evolution of the sampling technique and the changing indications for the procedure. The two important technical advances were the switch from using the vessels on the chorionic plate of the placenta as a source of blood to those in the umbilical cord when the fetoscope was being used[5] and, subsequently, the abandonment of the fetoscope for a percutaneous introduction of the blood sampling needle during ultrasound imaging.[6]

The changing indications for diagnostic fetal blood sampling, apart from its use in conjunction with fetal therapy, reflect changing diagnostic technologies and different diagnostic questions. Today there is a rapidly increasing ability to diagnose genetic disorders by the analysis of DNA, rather than having to depend on gene products or altered metabolism. The fetal genome is present in amniocytes and chorionic villus cells; genes can be studied whether or not their products are synthesized in those cells. Thus, we no longer need blood to analyze the hemoglobin molecule or measure clotting factors. Instead, we can analyze the globin genes or the genes for clotting factors.

An increasing indication for fetal tissue is the clarification or refinement of chromosomal diagnoses. Chromosomal mosaicism occurs in both amniocytes and chorionic villus cells at a low rate. At times cells directly from the fetus are desired to improve the interpretation. Mosaicism can never be completely excluded, however, so a level of uncertainty always remains. Also, for a few chromosomal trisomy disorders, it appears that blood cells are unlikely to express mosaicism even though it is present in other tissues; this is probably true for trisomy 7 and trisomy 20. Further investigation of mosaicism with these trisomy defects might call for a skin biopsy instead of, or in addition to, blood sampling.

In recent years it has become possible to look to fetal blood for evidence of an active infection. The immune response of the fetus, hematologic evidence of infection, and liver chemistries have all proved useful in this regard. Experience with both rubella and toxoplasmosis has been encouraging as to the accuracy of diagnosis.

When we accept the unborn baby as a patient, we must also look to the safety of our diagnostic and therapeutic interventions. As reported by Golbus and associates, the risk of fetal blood sampling has dropped as advances have been made in the sampling technique. In the hands of experienced perinatologists, the risk of fetal loss is approaching the risk with amniocentesis. Risks associated with several therapies are also low. These include the use of high-dose vitamin therapy through the mother in a few rare inborn errors of metabolism, administering cardioactive drugs, and transfusion through the umbilical vessels. Less safe or less efficacious have been attempts at the placement of shunts into the fetal body or other surgical interventions. Safety continues to improve, though, in all areas of fetal medicine even as the range of possible diagnoses and therapies expands rapidly. The needs of our unborn patients have become more clearly known to us, and concerted efforts to meet those needs continue to be forthcoming.

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Case Reports

Familial Thyrotoxic Periodic Paralysis

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THE ASSOCIATION OF Graves' disease and periodic paralysis was recognized as early as 1902[1] and defined as a distinct clinical disorder in 1926.[2] Thyrotoxic periodic paralysis, unlike familial periodic paralysis, is usually sporadic in occurrence. Several cases of patients with familial periodic paralysis in whom Graves' disease developed have been reported and likely represent the concurrence of two diseases.[3] Only two kindreds with Graves' disease and de novo periodic paralysis have been reported in the literature.[4,5] We report on two brothers who were simultaneously found to have Graves' disease presenting as periodic paralysis whose father had the same syndrome 25 years previously.

Report of Cases

Case 1

The patient, a 26-year-old Filipino-Chinese serviceman, was referred to the endocrine clinic for evaluation of hyperthyroidism. Seven weeks previously, after an afternoon game of basketball, he noted cramps in both quadriceps muscles before retiring. He awoke at 2 AM to urinate but was unable to move his arms or legs. He presented to an outlying military clinic where he was found to be diffusely weak and hyporeflexic with otherwise nonfocal findings on a neurologic examination. The weakness gradually resolved over a 12-hour period, but he continued to have recurrent attacks of paralysis preceded by cramps in the thighs. The episodes typically occurred at night, especially after physical exertion, and resolved by the morning. He was seen on several occasions at military sick call with complaints of weakness, and the results of a thyroid profile done to evaluate this were suggestive of hyperthyroidism. On presentation to Letterman Army Medical Center (San Francisco), he reported nightly paralysis and a six-month history of anxiousness, hyperhidrosis, tremor, dyspnea on exertion, hyperdefecation, and a 13.6-kg (30-lb) weight loss. His mother was Chinese and had enjoyed good health. His father, a Filipino, had a similar paralytic illness at the age of 29 that was cured by thyroidectomy. One of his brothers, also on active duty, had recently complained of an isolated nocturnal paralytic episode. No other history of either thyroid disease or paralysis was reported in the maternal siblings. The father lives in the Philippines, and a more detailed history is unobtainable.

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On examination the patient was clinically thyrotoxic with resting tachycardia, moist skin, bounding pulses, mild exophthalmos, tremor, and a diffusely enlarged thyroid. A thyroid panel elicited the following values: thyroxine (T_4) 26 μg per dl (normal, 5.5 to 11.2), triiodothyronine (T_3) uptake 42.4% (35% to 45%), free thyroxine index (FTI) 12.3 (1.9 to 5.0), and no detectable thyroid-stimulating hormone (TSH).* Radioactive iodine uptake at 24 hours was 74%. He was admitted to hospital for observation, and a regimen of propylthiouracil and propranolol hydrochloride was initiated. The admission potassium level was 4.5 mmol per liter (3.5 to 5.0). On the second hospital day he experienced his typical nocturnal paralysis with a simultaneous serum potassium level of 2.1 mmol per liter. He continued to have nightly paralysis despite increasing doses of propranolol and a subsequent trial of acetazolamide. The paralytic attacks lessened in severity and eventually were aborted with the administration of 60 to 80 mEq oral potassium at the start of muscle cramping. He was discharged with adequate control on a regimen of propranolol, propylthiouracil, and oral potassium as needed. Three weeks later the T_4 value was 14.6 μg per dl, the paralytic episodes had ceased, and he was treated with radioactive iodine ablation. After becoming euthyroid, he has had no paralysis off all medical therapy.

Case 2

The patient, the 24-year-old brother of patient 1, was contacted by one of us (W.M.K.) and asked to report to Letterman for evaluation. He related three previous episodes of nocturnal paralysis that resolved by morning. He also had a three-month history of fatigue, anxiousness, palpitations, and hyperhidrosis. On physical examination he had diffuse thyromegaly, resting tachycardia, moist palms, and hyperreflexia. His T_4 level was 18 μg per dl, the T_3 uptake was 43.5%, FTI 8.1, and the TSH was not detectable. Nuclear medicine studies showed a 24-hour iodine uptake of 81% and a diffuse scan. After admission, he had two episodes of nocturnal paralysis with serum potassium levels of 2.1 and 2.6 mmol per liter compared with morning values of 5.1 and 4.5 mmol per liter, respectively. A regimen of propranolol, propylthiouracil, and potassium was given at the start of muscle cramping, and he had no further paralysis. Four weeks later he was completely asymptomatic and was treated with radioactive iodine thyroid ablation. He is currently asymptomatic off all medical therapy.

Case 3

The father of patients 1 and 2, currently living in the Philippines, had a similar syndrome at age 29, confirmed by his wife, that lasted a year and has not recurred following a thyroidectomy. He currently takes thyroid hormone.

Discussion

The association of periodic paralysis and Graves' disease was first reported by Rosenfeld in 1902[1] and fully defined by Shinosaki in 1926.[2] To date, it has not been reported in association with other forms of thyrotoxicosis. As in familial periodic paralysis, it presents with episodic paralysis that

*The values for the thyroid function studies reported here are nonstandard and therefore have not been converted to SI units.

ABBREVIATIONS USED IN TEXT

FTI = free thyroxine index
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

often recurs after vigorous physical exercise or carbohydrate loads. The paralysis is typically nocturnal, may have a prodrome of cramping in affected muscle groups, and is characterized by relentless weakness progressing to paralysis. Proximal muscles are most severely affected, particularly the shoulders, back, iliopsoas, and quadriceps. Facial and smooth muscles (sphincters, viscera) are spared. During paralysis there is loss of the muscle stretch reflexes while sensation and mentation are unaffected. The paralysis typically persists for 6 to 12 hours untreated, although episodes lasting several days and death from respiratory failure have been reported in patients with familial periodic paralysis.[3] Electromyography of both disorders during attacks reveals decreased evoked potential amplitudes and increased single motor unit amplitudes characteristic of a myopathic disorder.[6] Electron-microscopic examination of affected muscle reveals dilated sarcoplasmic reticulum with numerous blebs suggesting increased pinocytotic activity.[7] The significance of these observations is unknown.

There are clear differences in familial periodic paralysis and the thyrotoxic form. While there are hypokalemic, hyperkalemic, and normokalemic variants of familial paralysis, thyrotoxic periodic paralysis is invariably associated with hypokalemia. The disease is sporadic in the vast majority of cases of the thyrotoxic form in contrast to the familial form. Only two kindreds with Graves' disease and episodic paralysis without a prior history of familial paralysis have been reported.[4,5] Our case is the first report of simultaneous thyrotoxic periodic paralysis in a kindred. The onset of familial periodic paralysis peaks in the first and second decades, while the incidence of thyrotoxic periodic paralysis parallels the occurrence of Graves' disease with peaks in the third and fourth decades.[8] The thyrotoxic form of episodic paralysis, though rare in whites and blacks, is fairly common in Asian men. In a series of 6,000 Japanese with thyrotoxicosis, 2% reported paralysis, with 8% of men and 0.4% of women afflicted.[9] A similar observation in a large population of Chinese with Graves' disease found the incidence of periodic paralysis to be 13% in men and 0.2% in women.[8] Ultimately the most important difference in the two variants of episodic paralysis is the ability to cure thyrotoxic periodic paralysis by achieving the euthyroid state either surgically, pharmacologically, or with radioactive iodine.

The precise pathophysiology of familial hypokalemic periodic paralysis and thyrotoxic periodic paralysis is unknown. Similar observations of both disorders suggest the relation of an intracellular shift of potassium to the development of muscle membrane refractoriness. Historical observations during episodes include the following:

- Hypokalemia;
- Decreased urinary excretion of potassium during paralysis and an absence of increased amounts of stool potassium, supporting the concept of an intracellular shift rather than a total body loss of potassium;
- Muscle-arteriovenous disparity of serum potassium levels, suggesting an intracellular shift;
- Precipitation of paralysis by factors known to cause an intracellular shift of potassium including carbohydrate loads, insulin, rest after exercise, epinephrine, and alkalosis;
- The ability to ameliorate paralysis by administering potassium at the onset of symptoms; and
- Spontaneous reversion to normokalemia with a resolution of paralysis without treatment.

These observations point to the importance of potassium, although the mechanism is unclear. The theory that an intracellular shift of potassium caused membrane hyperpolarization and subsequent refractoriness is disputed by in vitro microelectrode studies documenting hypopolarization.[10,11] The activity of the calcium pump mechanism in the sarcoplasmic reticulum is reduced during paralysis, and the reduction correlates with the severity of paralysis. Whether this represents a separate or a related phenomenon to the cationic shifts is unknown.[12] Engel and Lambert restored contractile function in electrically refractory muscle by the intracellular addition of calcium,[13] and Gordon and co-workers reported the close correlation of muscle tension and measured muscle action potentials during attacks, further supporting the notion that a failure of propagation of the action potential is the underlying defect rather than the contraction coupling mechanism.[14] To date, the exact pathophysiology and the role of thyroid hormone remain uncertain.

Thyrotoxic periodic paralysis is ultimately resolved by treating the underlying Graves' disease. Several modes of therapy have been suggested to decrease paralytic attacks in the interim. The most effective appears to be the administration of substantial doses of oral potassium salt, 60 to 80 mEq, immediately on cramping of muscle.[4,15] The regular administration of potassium is not as effective and carries a risk of hyperkalemia. Patients who do not report prodromal cramps and who awake with paralysis may benefit from the empiric administration of potassium on retiring.[16] Acetazolamide has been useful in patients with familial periodic paralysis—hypokalemic, hyperkalemic, and normokalemic variants[17]—but has no efficacy and may worsen episodes in those with thyrotoxic periodic paralysis.[18] Yeung and Tse and Conway and associates have found the use of propranolol reduces the frequency and severity of paralytic attacks in patients with the thyrotoxic form.[18,19] The mechanism by which propranolol decreases paralysis is unknown. Williams and colleagues recently showed the effects of both α- and β-blockade on the normal exercise-induced variation of the serum potassium level in a small group of healthy volunteers.[20] β-Adrenergic blockade caused an exaggerated rise in serum potassium levels with exercise that persisted in the postexercise period when potassium values normally return to baseline or slightly below. Blocking the β-receptor-mediated intracellular movement of potassium ion might explain the beneficial effect of propranolol on the paralysis of thyrotoxic periodic paralysis. Our cases were treated with propranolol, and while patient 1 continued to have periodic paralysis initially, he eventually became asymptomatic at a point where he was still biochemically hyperthyroid but clinically less thyrotoxic. Patient 2 was less thyrotoxic on discovery and responded initially to the institution of propranolol therapy with a resolution of the paralysis. Both patients were able on at least one occasion to abort full-blown paralysis with oral potassium salt, experiencing cramps but no further progression of the syndrome. Acetazolamide was tried in patient 1 during the initial period of frequent noc-

turnal paralysis but did not appear to influence his course. Paralytic episodes ceased in both patients after they became euthyroid on propylthiouracil therapy and have not recurred following successful radioactive iodine ablation. Finally, although paralysis is no longer apparent, the intrinsic defect remains and paralysis will recur with either recurring Graves' or iatrogenic hyperthyroidism.[21,22]

Due to the rare familial appearance of this disorder, we obtained human leukocyte antigen studies and compared them with previous reports in the literature. The following antigens were shared by both brothers: A24, B13, Bw4, Cw3, DR2, DQw1. Tamai and co-workers in a large population of male Japanese patients found DRw8 to be significantly more prevalent in patients with thyrotoxic periodic paralysis compared with patients with only Graves' disease.[23] Yeo and associates found A2, B40, Bw22, and Bw46 to be shared by two Chinese with thyrotoxic paralysis.[24] Kelly and Fishman reported a black man with A23, B14, and B15.[25] Valenta and colleagues similarly found A23 in a black woman with the disorder.[26] It appears that no histocompatibility antigen is universally associated with this disorder despite isolated reports suggesting some association in specific races.

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Paraneoplastic Cerebellar Degeneration Due to Hodgkin's Disease

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PARANEOPLASTIC CEREBELLAR DEGENERATION is a rare yet well-described consequence of systemic malignancy. Seen most commonly in tumors of the lung and ovary, it may also complicate the course of cancers of the breast, uterus, stomach, colon, and larynx. It was first described pathologically in Hodgkin's lymphomas by Malamud.[1(p302)] Progressive ataxia, vertigo, nystagmus, and dysarthria are its clinical hallmarks.[2]

We report the case of a patient who had a pure cerebellar syndrome as the sole manifestation of Hodgkin's disease. He was treated with conventional radiation therapy, and his neurologic syndrome abated dramatically. In a review of previously reported cases that had clinical data available, we found only one other case of such a dramatic improvement after therapy.[3]

Report of a Case

A previously healthy 31-year-old man presented in March 1986 because for the past two weeks he had had vertical diplopia and "vibrating vision" on left lateral gaze. He had had no previous illnesses or hospital admissions. He was taking no medications and his family history was negative. A review of systems was notable for slurring of speech and oscillopsia. In addition, the patient complained of general clumsiness and an unsteady gait.

The results of the general physical examination were unremarkable except for a palpable lymph node in the left supraclavicular fossa. On neurologic examination he had bilateral, horizontal, gaze-evoked nystagmus, with an upbeat component on gaze to the left. On cerebellar testing he had a pronounced intention tremor and dysdiadochokinesia of the left upper extremity and bilateral oscillation with the heel-to-shin maneuver. His gait was wide-based and unsteady, and his speech was mildly dysarthric.

Laboratory tests showed normal values for the hemogram, erythrocyte sedimentation rate, electrolytes, and liver and renal function tests. Assays for fluorescent antinuclear antibody and rheumatoid factor were negative. A serum protein electrophoresis was normal. The fluorescent treponemal antibody test was nonreactive. Serum titers for viral and

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic
MRI = magnetic resonance imaging

fungal pathogens were negative. An enzyme-linked immunosorbent assay for antibody to the human immunodeficiency virus was negative. A skin anergy panel was reactive, and the chest roentgenogram was normal.

Computed tomographic (CT) and magnetic resonance imaging (MRI) scans of the head showed no evidence of cerebellar atrophy. Brain-stem auditory-evoked responses, visual-evoked responses, and an electroencephalogram were normal. The cerebrospinal fluid (CSF) was under normal pressure with a glucose level of 3.3 mmol per liter (60 mg per dl) and a protein level of 490 mg per liter (49 mg per dl). The leukocyte count showed 35×10^6 per liter (0.14 segmented neutrophils, 0.81 lymphocytes, and 0.05 histiocytes), but a cytologic examination showed no malignant cells. A VDRL test for syphilis was nonreactive, and myelin basic protein was absent. The results of CSF electrophoresis were normal, with an immunoglobulin G index of 0.21 (normal, less than 0.25). All cultures, stains, and smears were negative.

Two months after his presentation, on May 29, 1986, a biopsy of the left scalene lymph node revealed nodular sclerosing Hodgkin's disease. A staging evaluation—including CT scans of the chest, abdomen, and pelvis; lymphangiography; bone marrow biopsy; and staging laparotomy—established that the patient's lymphoma was at stage II.

The patient underwent a course of standard radiation therapy (mantle and para-aortic). On follow-up neurologic examination two months later in July 1986, he still had the previously noted nystagmus; the tremor, dysdiadochokinesia, and gait problems, however, were totally resolved. The CSF findings had improved dramatically (see Table 1), and the cytologic examinations again did not show malignant cells. Specimens of CSF and serum were screened for anti-Purkinje cell antibody at the Mayo Clinic medical laboratory using an indirect immunofluorescence technique; these results were negative. Serial analyses of CSF for glucose, protein, and cell counts are summarized in Table 1. All viral, bacterial, and fungal cultures were persistently negative. Likewise, malignant cells were never found in the CSF.

TABLE 1.—*Laboratory Analysis of Cerebrospinal Fluid From Serial Lumbar Punctures*

Component	*3/5/86*	*5/12/86*	*5/19/86*	*5/27/86*	*7/25/86*
Protein, mg/liter*	600	560	490	360	380
Glucose, mmol/liter†	2.9	2.9	3.3	3.1	3.2
Cell count $\times 10^6$/liter (differential cell fractions)	28 (0.41 segmented neutrophils, 0.5 lymphocytes, 0.08 monocytes, 0.01 bands)	104 (0.1 segmented neutrophils, 0.77 lymphocytes, 0.13 monocytes)	35 (0.14 segmented neutrophils, 0.81 lymphocytes, 0.05 histiocytes)	42 (0.04 segmented neutrophils, 0.88 lymphocytes, 0.08 monocytes)	5 (1.00 lymphocytes)

*Normal value, 450 mg/liter.
†Normal value is two thirds of serum glucose value, or 2.8 to 4.4 mmol/liter.

TABLE 2.—*Clinical and Laboratory Data on Previously Reported Cases of Paraneoplastic Cerebellar Degeneration*

Source	*No. of Cases*	*Cerebrospinal Fluid*		*APCA*	*Imaging Studies*	*Syndrome Duration Before Hodgkin's Disease Diagnosed, mo*	*Cerebellar Signs Respond to Treatment*
		*Cellularity, $\times 10^6$/liter**	*Globulin*				
Malamud, 1974[1]	1	NR	NR	NR	NR	NR	No
Froissart et al, 1976[3]	1	12 (1.00 lymphocytes)	"Normal"	NR	NR	9	Yes
Brazis et al, 1981[5]	1	9 (1.00 lymphocytes)	"Normal"	NR	Cerebellar atrophy on CT	10	NR
Horwich et al, 1966[6]	1	1 (unspecified)	NR	NR	NR	4	No
Trotter et al, 1976[7]	1	2 (1.00 monocytes)	"Normal"	Present	NR	6	No
Tsapatsaris et al, 1979[8]	1	243 (0.87 lymphocytes)	NR	NR	Normal	2-3	No
Rewcastle, 1963[9]	1	"Acellular"	NR	NR	NR	5	NR
Ludmerer and Kissane, et al, 1985[10]	1	"Normal"	NR	NR	Normal	4-5	NR
Cunningham et al, 1986[11]	5	NR	NR	Absent	NR	NR	NR
Jaeckle et al, 1983[12]	1	NR	NR	NR	NR	NR	NR
Brain and Wilkinson, 1965[13]	1	6 (1.00 lymphocytes)	NR	NR	NR	8†	NR
Croft and Wilkinson, 1969[14]	1	NR	NR	NR	NR	NR	NR
Valtysson et al, 1979[15]	1	6 (1.00 mononuclear)	"Normal"	NR	Normal	17	No
Victor and Ferendelli, 1970[16]	1	"Normal"	"First zone elevation of gum mastic curve"	NR	NR	2-3†	NR
Present case	1	35 (0.14 segmented neutrophils, 0.81 lymphocytes, 0.05 histiocytes)	"Normal"	Absent	CT normal, MRI normal	3	Yes

APCA = anti-Purkinje cell antibody, CT = computed tomography, MRI = magnetic resonance imaging, NR = not reported

*The figures in parentheses represent differential cell fractions.
†Years.

Discussion

This patient's clinical presentation is typical of paraneoplastic cerebellar degeneration with Hodgkin's disease. The pathogenesis of this disorder is unclear, but possible mechanisms include the production of toxic factor(s) by the primary malignant disease, viral infection, abnormal populations of leukocytes with neurotoxic effects, or antibodies that cross-react with tumor and neuronal antigens.[2,4]

Although rare, paraneoplastic cerebellar degeneration caused by Hodgkin's disease is well documented.[3,5-16] In Table 2 is a list of reported cases and available clinical data.

Several aspects of this case bear emphasis. First, few patients who have this disorder caused by Hodgkin's disease have responded to treatment of the underlying lymphoma. Froissart and co-workers reported the remarkable response of their patient to treatment with mechlorethamine hydrochloride (mustard), vincristine sulfate (Oncovin), prednisone, and procarbazine hydrochloride.[3] Other patients have shown either a steady progression of cerebellar signs or at best a halt in progression.

Second, the presence of anti-Purkinje cell antibody in patients who have paraneoplastic cerebellar degeneration due to systemic malignancy has been documented primarily in carcinoma of the breast and ovary.[2,7,11,12] Although one case of this antibody occurring in a patient with Hodgkin's disease has been reported,[7] the report was criticized by several authors because serum diluted to less than 1:100 results in nonspecific staining.[11] The negative result in our case would support the findings of most of the reports on the subject.

Third, we did not find any other report of MRI studies on patients with this disorder, although CT was done on four patients. The normal results from CT and MRI in our patient no doubt reflect the early diagnosis and treatment of his lymphoma (stage II disease) before cerebellar atrophy became prominent. This early treatment would also explain his good therapeutic response because pathologic specimens of paraneoplastic cerebellar degeneration in advanced disease have shown extensive loss of Purkinje cells and thinning of the granule cell and molecular layers.[9,13,16]

Fourth, other authors have not reported polymorphonuclear cells in the CSF.[3,5-10,13,15,16] The pronounced pleocytosis of the CSF in our patient cannot easily be explained. The patient was afebrile, we saw no "left shift" on the hemogram, and no paraspinal focus was evident. Notably, the change from polymorphonuclear forms to lymphocytes occurred without antibiotic therapy—this finding argues against an infectious cause. Tsapatsaris and colleagues reported 0.87 lymphocytes in their patient but did not comment on the remaining cell types.[8]

Finally, we recommend that patients who present with a florid cerebellar syndrome and a paucity of other physical signs should have a careful examination of the lymphatic system.

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Kinetic Treatment Tables

To the Editor: The article by Demarest and colleagues in the January 1989 issue[1] provides a useful basis for the application of the Kinetic Treatment Table (KTT). We advise caution, however, in the application of KTT for patients who are critically dependent on a mechanical ventilator. Our experience is that the 120 degrees' rotation of the KTT bed produces a constant torquing force on ventilator tubing that can lead to frequent disconnections at the endotracheal tube or tracheostomy connector. We tried a variety of tube fixation methods but were unable to prevent this problem. We have, therefore, excluded quadriplegics and other critically ventilator-dependent patients from KTT, which is unfortunate because they are patients who might benefit from this treatment modality.

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Pet Ferrets—A Hazard to Public Health and Wildlife

To the Editor: European ferrets—relatives of the polecat—are cute and playful, and they are becoming increasingly popular as pets. Indeed, they have been dubbed the "pop pet" of the 1980s. Their growing popularity, however, is viewed with alarm by numerous public health entities and animal care organizations. Among the organizations opposing the keeping of ferrets as pets are the Humane Society of the United States, the Defenders of Wildlife, the American Veterinary Medical Association, the Council of State and Territorial Epidemiologists, the US Animal Health Association, the California Department of Health Services, and the federal Centers for Disease Control. Despite the problems attendant to keeping these animals as pets, ferret proponents have been conducting a national campaign in the past two years to popularize these animals and to repeal laws banning the keeping of pet ferrets.

Ferret play frequently assumes the form of mock attacks, which may result in bites to humans. Serious bites may occur, especially if the animal is surprised or angered. Adults are usually able to quickly terminate such encounters and thereby limit injury. Infants, however, who often seem to be perceived by ferrets as prey, may suffer severe injury as a result of such attacks.[1,2] Ferrets sometimes unleash frenzied, rapid-fire bite and slash attacks on infants, usually on their heads and throats, and sometimes inflict hundreds of bites. The animals have been reported to then drink the victim's blood and eat the shredded tissues.[1-4]

In order to better define the nature and extent of ferret attacks and in response to requests for information from the Department of Fish and Game and the Department of Food and Agriculture, the California Department of Health Services in early 1986 solicited reports about ferret attacks from neighboring states, federal and local government agencies, and professional organizations. During the subsequent two years, information was obtained on 452 ferret attacks spanning the ten-year period 1978 through 1987.[1] A total of 425 attacks on people were reported from California, Oregon, and Arizona. Of these attacks, 100 were in California, where it has been illegal to keep ferrets as pets since 1935. Also reported from a total of 18 states were 63 unprovoked attacks on infants and small children. Several of these were near-fatal attacks. One additional case, a fatal attack, was reported from London.

Data from California indicate that the majority of attacks were inflicted by pet ferrets belonging to households other than the victim's.

In all, 28% of infants required plastic and reconstructive surgery, 22% of victims required rabies prophylaxis, and 4% were known to have been exposed to rabid ferrets.

Ferrets have a great propensity for escaping from their principal residences, and escaped ferrets are known to boldly approach wildlife. These ferrets may develop rabies after returning home; 12 such cases have been reported in the United States. There is no approved rabies vaccine for ferrets.

Ferrets also develop feral populations and are especially destructive of poultry and small wild animals such as rabbits, which was the reason why the keeping of ferrets as pets was outlawed in California. Data gathered from our survey, however, suggest greater surveillance and enforcement efforts in this regard may be needed.

Physicians should be aware of the problems associated with the keeping of pet ferrets—especially their hazard to infants—and the keeping of these animals as pets should be strongly opposed by medical and public health organizations.

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Corrections

To the Editor: I have an attribution problem in the article, "Chemical Dependency in Women," by Kathleen Bell Unger, MD, in the December 1988 issue.[1] It occurs on page 749 in Figure 3, which she attributes to Talbott, her reference 14.

The proper attribution is to the article by Melvin L. Selzer: Selzer, ML: The Michigan alcoholism screening test: The quest for a new diagnostic instrument. Am J Psychi-

atry 1971; 127:89-94. Talbott's article simply is a review of this original article. The reason I am being picky is that this reference of Dr Selzer's is one of the most widely quoted in the professional literature, especially the literature about alcoholism.

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To THE EDITOR: In my article, "Laboratory Evaluation of a Bleeding Patient,"[1] there is an error on page 51, right-hand column, third line from the bottom. It should read, "The thrombin time may be prolonged by a decreased amount of *or* dysfunctional fibrinogen or by substances that interfere with fibrin polymerization (Table 1)." It probably would have been clearer to have said "may be prolonged by reduced or dysfunctional."

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Cigarette Taxes—Regressive or Progressive?

To THE EDITOR: California voters recently passed Proposition 99, which imposed a new 25 cents per pack state tax on cigarettes. During the months before the vote, the tobacco companies launched an advertising campaign designed to convince voters to defeat the proposition. One argument raised by the tobacco companies concerned the regressivity of the tax. Two points were made. First, the percentage of a typical poor person's income spent on cigarettes is likely to be higher because all smokers' expenditures on cigarettes do not vary greatly but their incomes do. Most smokers smoke from 10 to 50 cigarettes a day, but the incomes of all American smokers display much more than a five-fold difference. Second, and more important, a much greater proportion of the poor than the rich smoke. Education is known to be strongly correlated with income and with cigarette consumption.[1] About 35% of high school dropouts—as opposed to 23% of people with college degrees—were smokers in 1985.[2] These two points can be summarized by aggregate statistics on the percentage of income all smokers and non-smokers who are poor spent on tobacco products versus that spent by all smokers and non-smokers who are rich. The percentage of income devoted to tobacco products among persons in the lowest quintile (fifth) of the income distribution in 1984 was 4.56%. The percent in the highest quintile was 0.45%.[3] Smokers and non-smokers who are poor spent approximately ten times more of their incomes on tobacco than did smokers and non-smokers who are rich. It is appropriate to include nonsmokers in the rich and poor categories because regressivity or progressivity is calculated on the basis of taxes paid by groups with varying income—not varying consumption.[4]

The tobacco company advertisements carefully ignored a closely related argument, however. The poor are more sensitive to increases in cigarette prices.[5] Teenagers, for example, earn far less than any other age group but are especially sensitive to increases in prices. Moreover, as prices increase, fewer teenagers are likely to ever begin smoking than persons in other age brackets.[6] The benefits of the tax in terms of discouraging smoking are likely, therefore, to be progressive. A disproportionate number of lives of the poor are likely to be saved by a cigarette tax.

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Health Care Delivery

Factors Associated With Physician Recognition and Treatment of Alcoholism

LAWRENCE S. LINN, PhD; *and* JOEL YAGER, MD, *Los Angeles*

We surveyed internists, family physicians, and psychiatrists regarding their clinical experiences in assessing and treating alcohol abuse, practice characteristics, political and religious beliefs, attitudes toward substance abuse, beliefs about the efficacy of treatment, personal experiences with substance use, and sociodemographic variables. Despite the high prevalence of alcohol abuse, a third of the physicians neither regularly counseled nor referred any patients for outpatient rehabilitation, and more than half had not referred anyone for inpatient treatment. A greater breadth of experience treating alcohol problems was positively correlated with the volume of outpatients and inpatients seen, younger age, more work in primary rather than specialty patient care, less academic work, a stronger belief in the efficacy of treating alcoholism, membership in the Republican party, and a greater religiosity.

(Linn LS, Yager J: Factors associated with physician recognition and treatment of alcoholism. West J Med 1989 Apr; 150:468-472)

The prevalence of alcoholism, alcohol abuse, or heavy alcohol consumption is widespread, and the morbidity, mortality, property damage, and lost productivity attributable to alcohol misuse are enormous. Despite the magnitude of this important social and medical problem, it has recently been noted that although 10% of all adults entering a physician's office are likely to have an alcohol problem, this is seldom recognized or treated.[1,2]

Because recent studies have indicated that adults in the United States visit physicians an average of four times a year, physicians are in an excellent and unique position to identify the abuse of alcohol by their patients. Although most problem drinking goes undetected, some physicians may be more attentive and vigilant than others in recognizing substance abuse problems. To date, however, little information exists about whether physicians who recognize and treat alcohol abuse problems in their clinical practice have attitudes, beliefs, or other characteristics that distinguish them from physicians who tend not to recognize or treat alcoholism.

To examine this recognition process, we initiated an exploratory study that addressed the following questions: How frequently, if at all, do practicing physicians report recognizing, treating, and referring their patients for alcohol abuse? and What kinds of physician attitudes, beliefs, attributes, or experiences are related to rates of recognition? We developed and tested an explanatory model in which rates of recognition were hypothesized to be a function of the following categories of variables: sociodemographic characteristics, practice characteristics, political and religious beliefs, attitudes toward substance abuse and the efficacy of treatment, and personal experiences with substance use. Identifying subgroups of the physician population more or less likely to deal with the alcohol problems of their patients should be useful in understanding barriers that inhibit recognition and treatment, as well as help determine which physician subgroups might be most in need of continuing medical education or other interventions.

Methods and Measurements

Sample and Design

During the summer of 1987, all full-time academic physician faculty of the Departments of Medicine and Psychiatry at UCLA were asked to complete self-report questionnaires that required about 45 minutes of their time. Also, all practicing clinical faculty affiliated with those departments whose specialty was general internal medicine, family medicine, gastroenterology, or psychiatry were sent the same questionnaire. Because of the sensitivity and personal nature of some of the questions in the survey, respondents were guaranteed confidentiality and anonymity. Questionnaires were sent to all respondents twice, one month apart, because our research design included fully anonymous responses and did not permit a determination of which physicians had responded to the initial mailing. Of the 629 questionnaires sent, 21 were returned by the post office. Of the 608 remaining surveys, 303 were completed and returned, constituting a 50% response rate.

Respondents had the following characteristics: 91% were white, 87% were men, 85% were married, and 39% were academically based, full-time faculty. About half were board certified in internal medicine, 24% in psychiatry, 14% in family medicine; 12% were not board certified. The average age was 48 years, and they had worked in their current job an average of 14 years. Based on our initial mailing rosters,

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Reprint requests to Lawrence S. Linn, PhD, Division of General Internal Medicine, UCLA Center for Health Sciences, Los Angeles, CA 90024-1685.

TABLE 1.—*Physician Estimates of Their Experiences With Alcoholic Patients Over the Past Year (n=303), %*

Type of Patient Experience*	Number of Alcoholic Patients				
	0	1-3	4-6	7-9	≥10
Drinking seriously interfered with health	12	26	16	11	35
Patients diagnosed as alcoholic who had not been previously diagnosed	29	37	15	6	13
Referred to an outpatient treatment program	31	31	16	6	17
Counseled about drinking on 3 or more visits	34	30	16	7	13
Referred to an inpatient treatment program	52	33	4	4	8

*Five items were used to construct the Physician Experience with Alcoholism scale.

nonrespondents were somewhat more likely to have been in full-time community-based practice than in a full-time academic setting. No differences in specialty or sex were found among respondents and nonrespondents. Also, the average age of respondents was similar to the age of respondents in a survey previously conducted in this same physician population in which a considerably higher response rate was attained.[3]

Sociodemographic Characteristics, Work Roles, and Practice Characteristics

In addition to sex, marital status, age, number of children, and ethnic or racial identity, physicians also described their current affiliation with a teaching hospital or medical school, their board-certification status, the length of time in their current job, the average number of hours they worked per week, how much vacation time they had taken in the past year, and how many inpatients and outpatients they had cared for in the past two weeks. Finally, they described their medical practices in terms of the amount of specialty versus primary care, the kind of practice arrangement in which they spent most of their time, the number of articles they had published in scholarly journals, and their estimated percentage of time spent in administrative work, teaching, house-staff supervision, research, and direct patient care over the past year.

Political and Religious Beliefs and Attitudes Toward and Experience With Drug Use and Treatment

Physicians indicated their attitudes toward government regulation of the medical profession on a previously validated scale[4] and indicated their political orientation—radical left, liberal, middle-of-the-road, conservative, or radical right—and political party affiliation. They also indicated how religious a person they thought themselves to be.

Physicians' attitudes toward the degree to which they felt there was a drug problem were measured by a four-item scale (Cronbach's α-reliability coefficient is .57). Their attitudes toward the degree to which physicians in general needed to be more aggressive in diagnosing and treating substance abuse problems were also measured by a four-item scale (α .74). Attitudes toward the legalization of drugs were measured by a six-item scale (α .91). Additionally, two scales developed by Chappel and co-workers[5] and adapted to our study were used to measure attitudes toward the effectiveness of treatment for alcoholism—a Treatment Optimism scale and a Treatment Intervention scale: α .51 and α .54. Three indices were also constructed that measured physicians' attitudes toward the permissibleness of using alcohol, marijuana, and cocaine in a variety of situations. Finally, we measured these physicians' personal experiences with and use of beer, wine, and hard liquor (α .62), as well as their experiences using marijuana, cocaine, and amphetamines (α .62). Copies of all scales are available from the authors.

Clinical Experience With Alcoholism

In measuring our dependent variable, we asked physicians to estimate the number of patients they had seen over the past year whose drinking seriously interfered with their health, whom they had diagnosed as being alcoholic but who had not been previously diagnosed by another physician, whom they referred to an outpatient alcoholic rehabilitation program, whom they regularly counseled about their drinking in three or more visits, and whom they successfully referred to an inpatient alcoholic rehabilitation program. Physicians were given five response categories in which to place their estimates: 0 patients, 1 to 3, 4 to 6, 7 to 9, and 10 or more.

Results

Our physician sample reported a wide variation in their attention to and treatment of alcoholism in their routine clinical practice (Table 1). Although most (62%) reported seeing four or more patients over the previous year whose drinking had seriously interfered with their health, physician involvement with diagnosis, treatment, or referral was considerably less. For example, nearly 30% of the sample reported never having diagnosed an alcohol problem not previously diagnosed by another physician, and about a third had neither regularly counseled patients about their drinking nor had referred anyone for outpatient rehabilitation. About half (52%) had never referred a patient for inpatient treatment of alcoholism during the past year.

To determine the internal consistency of the five items presented in Table 1, we calculated a Cronbach's α-coefficient of reliability. The results indicated that the five items constituted an extremely reliable scale of experience with alcoholism, the Physician Experience with Alcoholism (PEA) scale, with an α of .89. We also dichotomized physician responses to the items in the PEA scale into those who had seen at least one patient and those who had seen none for each of the five criteria. Thus, respondents' scores could range from 0 to 5. We calculated the α-reliability coefficient for this method of scoring to be .82. Of the sample, 10% had not seen a single patient who met any of the five criteria, 8% had seen one or more patients for only one of the five criteria, 10% for two criteria, 10% for three criteria, 24% for four criteria, and 37% had seen at least one patient in all five situations. This version of scoring the PEA scale will be the focus of ensuing analyses because it reflects the breadth of experience working with alcoholic patients rather than emphasizing the volume of experience.

PEA Scores and Sociodemographic Characteristics

Table 2 shows either F-test scores based on one-way analyses of variance or χ^2 values between physicians' PEA scale scores and all study variables. More specifically, this table shows that experience with alcoholic patients over the previous year was unrelated to a physician's marital status, sex, ethnic background, or the number of children he or she had. Younger physicians were significantly more likely to have worked with alcoholic patients than were older physicians, however.

PEA Scores and Physicians' Work Roles and Practice Characteristics

Table 2 clearly shows that physicians who reported more diverse experience diagnosing and treating alcoholism were significantly more likely to have been working in high-volume, community-based primary care practices and were significantly less likely to be engaged in academic or scholarly pursuits. Higher PEA scores were significantly correlated with having seen more outpatients and inpatients in the previous two weeks, having spent a greater percentage of time in primary versus specialty care, and having spent a greater percentage of the work week in direct patient care. Higher scores were negatively associated with time spent in administrative activities, classroom teaching, and research, as well as negatively related to the number of published scientific articles. Finally, physicians who were board certified in family medicine reported having had more diverse experience working with alcoholic patients than board-certified internists or uncertified physicians. Board-certified psychiatrists and subspecialists were significantly less likely to report having had such patient experiences. The PEA scale scores were unrelated to physicians' length of employment in their current job, hours worked per week, amount of vacation taken, or time spent supervising house staff.

PEA Scores and Physicians' Attitudes, Values, Habits, and Experience

Only a few attitudes and experiences of physicians were significantly associated with their breadth of experience di-

TABLE 2.—*The Relationship Between PEA Scores (0-5) and Study Variables*

	Number of PEA Score Criteria								
Variables	*None*	*1*	*2*	*3*	*4*	*5*	*F/χ^2 Test*	df	P
Sociodemographic									
Age, years	53.4	51.8	49.5	46.1	47.1	45.3	3.29	5/282	<.01
Sex, % male	76	96	83	79	88	91	7.84	5	NS
Marital status, % married	93	96	87	86	79	85	5.5	5	NS
Number of children	2.5	1.8	2.0	2.0	2.1	2.0	0.69	5/277	NS
Race, % white	93	91	86	90	88	93	2.64	5	NS
Work roles and practice characteristics									
Board certified in Medicine, %	41	65	57	41	58	43	8.36	5	NS
Board certified in Psychiatry, %	28	22	27	48	15	24	12.65	5	.05
Board certified in Family Medicine, %	3	0	0	7	19	22	20.17	5	<.001
Board certified in subspecialty, %	28	65	33	39	23	19	23.17	5	<.0001
Years in current job	18.4	15.2	13.6	13.2	14.2	13.7	1.01	5/281	NS
Hours worked per week	51.4	59.0	57.5	52.7	55.6	55.7	1.25	5/281	NS
Vacation days in past year	22.3	20.6	16.1	17.1	20.5	17.9	1.4	5/282	NS
Inpatients seen past 2 weeks	4.1	1.6	4.9	3.0	5.9	7.8	3.95	5/283	<.01
Outpatients seen past 2 weeks	27.3	19.3	30.1	40.3	78.2	112.3	14.84	5/280	<.0001
Degree of specialty *vs* primary specialty care	4.2	4.3	3.9	3.8	2.9	2.7	9.25	5/279	<.0001
Articles published, No.	77.5	73.0	35.7	27.8	11.6	8.7	9.1	5/277	<.0001
Time in administration, %	17.4	25.1	15.2	18.4	12.1	8.8	5.0	5/284	<.001
Time teaching, %	4.8	2.7	4.3	4.5	2.1	2.3	2.79	5/284	<.02
Time supervising house staff, %	9.1	12.6	14.7	11.2	8.3	9.2	1.78	5/284	NS
Time doing research, %	25.0	25.5	20.7	13.6	8.5	3.1	14.2	5/284	<.0001
Time in patient care, %	32.7	24.7	36.6	46.7	61.5	68.0	17.3	5/284	<.0001
Practice setting, % teaching hospital	52	74	67	48	29	17	50.29	5	<.0001
Attitudes, Beliefs, and Experience									
More federal regulation	2.8	2.6	2.9	2.6	2.6	2.6	2.28	5/280	<.05
Politically conservative, %	10	9	3	17	19	20	6.8	5	NS
Republican, %	7	9	3	17	22	26	13.56	5	.02
Drug problem in United States	4.2	4.1	3.9	3.9	4.0	4.0	0.58	5/283	NS
Physician aggressiveness in substance abuse	3.5	3.6	3.4	3.7	3.5	3.8	1.82	5/284	NS
Legalize drugs	2.4	2.2	2.2	2.2	2.0	2.0	1.91	5/278	NS
Treatment optimism	3.7	3.6	3.7	3.7	3.7	3.8	0.98	5/282	NS
Efficacy of intervention	4.1	4.0	3.8	4.0	4.0	4.2	3.2	5/282	<.01
Personal use of alcohol	3.4	3.9	4.0	4.0	3.6	3.6	2.17	5/276	NS
Personal use of marijuana, cocaine, and amphetamines	1.2	1.3	1.3	1.5	1.4	1.5	1.81	5/278	NS
Religiosity	3.9	4.2	4.2	3.9	3.7	3.5	3.46	5/283	<.01
Attitudes toward alcohol use	12.3	12.4	13.2	13.8	13.6	13.4	0.69	5/282	NS
Attitudes toward marijuana use	4.3	5.6	7.4	6.1	5.9	7.1	1.16	5/281	NS
Attitudes toward cocaine use	0.3	0.5	1.3	1.4	0.7	2.6	2.38	5/280	<.05

NS=not significant, PEA=Physician Experience with Alcoholism [scale]

agnosing and treating alcoholic patients (Table 2). For example, physicians with higher PEA scale scores were more likely to be religious and to be a member of the Republican party and less likely to favor federal regulation of the medical profession. Physicians with higher scores were also more likely to feel that alcoholism could be treated effectively. The PEA scores were not associated with political orientation or with beliefs about the extensiveness of the drug problem in the United States, the degree to which physicians should aggressively treat alcoholism, or attitudes toward legalizing drug use, however. Recognizing and treating alcoholism were unrelated to physicians' current or previous use of beer, wine, hard liquor, or other drugs. Their PEA scale scores were also unrelated to attitudes toward what constituted acceptable social uses of alcohol or marijuana. Physicians with higher PEA scale scores, however, expressed more liberal attitudes toward the use of cocaine.

Multivariate Analysis

To determine how much variance in PEA scale scores could be explained by the variables we studied, we did a stepwise multiple linear regression analysis. The 18 variables listed in Table 2 with an association of .05 or greater with PEA scale scores were entered into the analysis. As Table 3 shows, 8 of the 18 variables explained 42% of the variance in physicians' reported breadth of experience in working with alcoholic patients. No significant amount of additional variance was explained by entering the other ten variables into the regression equation. Physicians who were more heavily involved in scholarly activity, as reflected by their time spent doing research and the volume of their publications, were less likely to diagnose, treat, or refer patients for the treatment of alcoholism. Conversely, physicians who were more heavily engaged in primary patient care and who saw more patients were significantly more likely to report a greater breadth of experience working with alcoholic patients, as were physicians who were younger, members of the Republican party, and who were not psychiatrists. Thus, work roles, practice characteristics, and age explained most of the variance in the breadth of work experience with alcoholism. Once these factors were taken into account, the personal habits, beliefs, and attitudes that we measured explained no additional variance in the scope of activities that physicians reported.

Discussion

Hospital-based studies of the prevalence of alcoholism have revealed rates of from 4% to 9% for women and from 15% to 29% for men.[6-9] Similarly, results from the Epidemiologic Catchment Area Studies in five US communities indicated that substance abuse among men using medical services ranged from 5% to 14%, underscoring the need to increase the ability of general medical practitioners to recognize, manage, or refer these conditions.[10] The results of our survey confirm these previous studies (Table 1). Given the large number of patients seen by clinically active physicians during an average year, together with the prevalence of alcoholism among patients who seek medical care, our results clearly reflect how serious a problem the underdiagnosis and undertreatment of alcoholism might be among practicing physicians. We also found that the recognition, treatment, and referral of alcoholism varied widely among physicians with different work roles and practice characteristics.

TABLE 3.—*Summary Table of Stepwise Linear Regression on PEA Scale Scores*

Significant Variable	*r*	R^2	*F Test to Enter*
Time spent in research, %	.445	.198	65.78
Age	.528	.279	29.76
Number of outpatients seen	.578	.334	21.62
Number of published articles	.595	.354	8.10
Member of Republican party	.608	.370	6.77
Number of inpatients seen	.618	.382	5.09
Board certification in psychiatry	.630	.397	6.31
Amount of primary *vs* specialty care	.650	.422	11.54

PEA=Physician Experience with Alcoholism

Similar to the results of a recent survey of British general practitioners,[11] our results show that a current use of alcohol by physicians was unrelated to their rates of recognizing and treating alcoholism, as were their attitudes toward and experience with using other drugs. Although political party membership and religiosity were found to be significantly associated with the treatment of alcoholism, the present study was not successful in identifying other ideologic pathways that motivate physicians to become clinically involved in treating alcoholism.

A second important set of findings involved the relationships between PEA scale scores and physicians' age, work roles, and types of practice. Although a cross-sectional survey such as ours does not permit causal inferences or the determination of the direction of associations, it is noteworthy that younger physicians were more likely than older ones to be diagnosing and treating alcoholism. We doubt that this zealousness among younger physicians can be attributed to any major changes in medical education, since recent reviews of alcoholism training for medical students and residents have found it less than adequate or effective.[12,13] The question of whether this zealousness of younger physicians in treating alcoholism will persist as their careers evolve cannot be answered by our data.

Our findings also provide some insight about the degree to which the teaching hospital is currently a viable learning environment for exposure to diagnosing and treating alcoholism. For example, physicians who spent most of their time in a teaching hospital, who spent more time engaged in research or teaching activities, who had published more scholarly articles, or who engaged in more specialized practice were significantly less likely to have diagnosed, treated, or referred alcoholic patients over the previous year. Thus, medical students or residents in the academic environment may be less likely to see alcoholism diagnosed and treated and are certainly less likely to encounter physician role models who have these skills. Our data further suggest that such role models are more likely to be encountered in high-volume, primary care-oriented practices of family physicians in the community. The findings that physicians in busy clinical practices were more likely to treat alcoholism and that rates of recognition were unrelated to how many hours per week physicians worked tend to refute the argument that diagnosing and treating alcoholism take too much time. The rate of missed diagnoses and the efficacy of physicians' treatment efforts are unknown, however. Finally, our findings are compatible with the observation that medical and surgical complications resulting from alcoholism are more likely to be treated than alcoholism itself[14] and that this might be most

likely to occur in the teaching hospital environment. Caution must be used, however, in generalizing our findings to physician populations in different specialties or geographic locations. Also, the PEA scale needs to be validated against measures of actual physician behavior. Clearly, additional studies are needed.

Our findings also suggest that physicians who had a greater breadth of experience treating alcoholism were significantly more likely to believe in what they were doing, feeling that such treatment was efficacious. The extent to which these attitudes determine their actions, rather than follow them, cannot be assessed from our data, although a similar finding was reported in the study of British general practitioners.[11]

Although we were able to explain 42% of the variance in physicians' reported recognition and treatment of alcoholism with the variables we studied, there were several potentially important areas that we did not address. For example, future studies might investigate whether recognizing and treating alcoholism are related to the amount and kind of previous medical school training and continuing medical education physicians had received in substance abuse. Also, the role of peer pressure to treat or not treat alcoholism within physicians' work environments, the availability of accessible and effective referral sources, and the role of financial reimbursement for recognizing and treating alcoholism in different work environments and patient populations need to be investigated.

One implication of our findings is that teaching hospitals must do more to integrate the diagnosis and treatment of alcoholism into the clinical and academic environments. Although this has been accomplished by many private hospitals, perhaps for financial reasons, teaching hospitals may also want to create inpatient and outpatient substance abuse treatment units like the program at Vanderbilt University (Nashville, Tennessee).[15] Besides providing needed patient services, these units, through their staff and patient referrals, may help educate other hospital-based physicians in diagnosing and treating alcoholism. Such units could also provide valuable educational opportunities for medical students and residents.

Finally, another implication of our findings is that continuing educational interventions to improve recognition and treatment skills should be targeted toward specific physician subgroups. Internists, psychiatrists, subspecialists, and older physicians need to be recruited into continuing medical education activities that raise their consciousness about alcoholism as well as improve their treatment skills.

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Medicine in Perspective

A Brief History of Graduate Medical Education in Washington, Alaska, Montana, and Idaho

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Internships and hospital-based medical education preceded by more than 40 years the beginnings of a medical school in Washington State. Just after the turn of the 20th century, a few internships were begun by hospitals in Seattle and Spokane to help with the care of their sicker patients in the tradition of Eastern teaching hospitals. In the 1920s and 1930s, the number of hospitals with internship programs grew steadily as part of a nationwide effort at hospital standardization. Experiences in developing these programs and problems with intern recruitment contributed to the beginning of the University of Washington School of Medicine after World War II. Since the 1960s, intern and resident training has progressively become a cooperative effort of the school with many hospitals and clinics in Washington, Alaska, Montana, and Idaho contributing to the development of graduate medical education in this region.

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A century ago there were only a few programs for graduate medical education in the United States, principally in teaching hospitals in the major Eastern cities.[1] In the late 19th century, the number of hospitals as well as the number of internships and residencies began to grow, related to the development of modern surgery and anesthesiology, changes in medical education, and advances in the scientific basis of medical practice. At this time the Pacific Northwest was sparsely settled and had few educational institutions or hospitals. Oregon had begun a medical school in 1887, but there were no medical education programs in the state of Washington. The first internships and hospital-based medical education were begun in Washington more than 40 years before a medical school was started. These early programs contributed in many ways to establishing a medical school of the University of Washington. This history shows the gradual and relatively recent development of medical education in the Western states and the unique relationships that have fostered the development of the University of Washington School of Medicine as a regional medical school.[2]

Background

The historic roots of our system of training interns and residents are traceable to the first formal system of hospital-based training established in England by the Society of Apothecaries in 1617.[1] Almost 50 years later, the London hospitals—St Bartholomew's, Guy's, St Thomas's, and others—were opened to medical students and apprentices, or "pupils" and "dressers." In 1744 the Royal Infirmary in Edinburgh appointed a "clerk of the house" with medical duties, as well as responsibilities for collecting tickets from students and fees from patients. By the late 18th century, young physicians working in Edinburgh were called "residents," the term later adopted by many of the founders of the early American medical schools who had trained there. "Intern" is the French term for this same position; it did not come into wide use here until early in the 20th century.

Soon after the opening of the first US medical schools (Pennsylvania, 1765; Columbia [New York], 1767; Harvard [Boston], 1782), a few hospitals began internship-type programs. In 1773 the Pennsylvania Hospital, which had opened in 1751, took on its first intern. Philadelphia General Hospital appointed four "house pupils" in 1789. The New York Hospital (1797) and the Massachusetts General Hospital (1820) were other early sites for graduate training.

Before there were any hospitals or internships in the Northwest, many of the present-day characteristics of graduate medical education had already been established. In a number of urban locations, hospitals accepted trainees who would supplement their medical education after receiving the MD degree while they assisted the hospital staff with the care of the sicker patients. In the mid-19th century, as these hospitals began to grow, divisions of labor began to occur, with more and more specific medical and laboratory responsibilities being assigned to interns and residents.[3]

There are no accurate records of the number of internships or residency positions before 1900. There are, however, numerous general descriptions of intern and resident training. Hospital appointments were made usually for a year but sometimes longer. A hospital often provided housing, clothing, and food but usually no salary. Interns worked very long hours. The education format was largely informal. Then as now, the most highly sought internships were in hospitals closely affiliated with medical schools. Interns worked with a variety of attending physicians and nurses. They provided patient care and spent some of their time teaching practical skills to medical students while learning the nuances of medicine from a variety of clinical teachers.[4]

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The Beginning of Hospitals and Internships in Washington

The first hospitals in the Northwest were begun in the 1870s. St Vincent's Hospital in Portland, the first hospital in the region, was begun by Mother Joseph of the Sacred Heart and the Sisters of Providence in 1875. In 1877 Seattle's first hospital was started with the arrival of three Sisters of Providence from Portland to operate a hospital for King County at the poor farm in Georgetown.[5] Because this facility was owned by the county and operated by the Sisters of Providence, it is the common origin of what are now the Providence Medical Center and the Harborview Medical Center. Although Seattle's first physician, Doc Maynard, had two rooms in his home where he and his wife, Katherine, cared for sick patients somewhat earlier, theirs could hardly have been called a hospital.[6]

In terms of medical education, there were no interns in the early days of the hospital at the poor farm, but the two institutions that emerged from this early health care facility later became important centers for training interns and residents. It is noteworthy that the Sisters of Providence not only began a hospital in Seattle, but soon thereafter, in 1886, they began a hospital in Spokane (Washington), the Sacred Heart Hospital, and a number of other health care institutions across the region, as well.[7]

The coming of the railroad, the Alaskan gold rush, and the rapid growth in Seattle's population in the 1880s and 1890s caused many changes in the city's population and its health care institutions. By 1883 efforts were underway to regulate medical practice in the territory, and an act of the legislature allegedly drove out many quack practitioners. The King County Hospital was expanded in 1885, and in 1887, the county commissioners began administering it themselves, with a complete separation from Providence, due in part to complaints from non-Catholics in the community.[5]

In 1895 the Seattle General Hospital was founded by a group of civic-minded women who thought the community needed a Protestant hospital. They were aided substantially by a miner who had struck it rich in the Klondike. In 1897 Seattle General, like many other hospitals across the country in this era, started a school of nursing. In 1902-1903, Seattle General accepted Frank T. Maxson, MD, to serve as the hospital intern. According to the records of the Office of Medical Education at Swedish Hospital Medical Center, Dr Maxson was the first graduate medical education trainee in the state of Washington.

The appointment of Maxson reflected the rapid changes in medicine that occurred in the last quarter of the 19th century and heralded the gradual but steady growth of graduate medical education in the region in the years to follow. At this time, modern basic medical sciences, hospital laboratories, and diagnostic techniques, particularly in radiology and cardiology, were all developing rapidly. From a clinical perspective, however, the most dramatic changes were occurring in surgery. The development of safe techniques for removing the appendix and gallbladder was having a major influence on hospitals everywhere. Throughout the country, surgical case loads increased dramatically. To meet the need for more beds, efforts were made to increase hospital efficiency and to abbreviate the length of hospital stays. Many new hospital-based nursing schools started because more nurses were needed. Many new hospitals were established, as well.[3]

As Paul Starr points out in his book, *The Social Transformation of American Medicine,* these changes in the characteristics of hospitals set the stage for important changes in the responsibilities and the training of physicians.[3] As the needs of patients in hospital became more medical and technical, the influence of physicians increased. They, rather than laypersons, decided who was sick enough to be admitted and who was well enough to leave. Because it was generally in the mutual interest of physicians and the hospital to operate efficiently and, if possible, profitably, interns often were added to make hospital stays go faster and smoother. This also helped hospitals wanting more patients to attract more physicians to the medical staff. Thus, in the first decade of this century, a critical change in graduate medical education happened. Interns were no longer just advanced students in a few teaching hospitals; they were in demand for their services and—almost everywhere—began to be paid.

Internships and Hospital Standardization

The first list of internships in the United States was published by the American Medical Association in 1914. At that time there were 11 such positions available at hospitals in Washington: the Northwest Sanitarium in Port Townsend (1); King County Hospital (1); Seattle City Hospital (3); Seattle General Hospital (2); Northern Pacific Hospital, Tacoma (2); and St Joseph's Hospital, Tacoma (2). Most of these appointments were for a year. Five of six offered some salary. Only the hospital of the Northern Pacific Railroad in Tacoma was listed as having a library. Records are scarce, but apparently several of these positions went unfilled.

A review of hospital records shows that there were some sporadic intern appointments in other hospitals before this date. For instance, in addition to the appointment of Maxson, Mary MacMillan Rodney, MD, was an intern at the Deaconess Hospital in Spokane in 1907-1908[8(p40)]; John Edward Godfrey, MD, interned at Providence in 1912-1913; and Albert Knutsen, MD, interned at Providence in 1913-1914. Godfrey's appointment at Providence was perhaps typical for the early interns in this area. He had graduated from the University of Toronto, Ontario, and came to Seattle from Washington, DC, where he had already been in practice for ten years. On arrival in Seattle, he learned that he had to wait six months until he could obtain a license. While waiting, he visited Providence and met Sister Vincent Ferrier, then the Sister Superior there. She invited him to serve as an intern, to be the hospital's anesthetist, and to direct work of the laboratory while waiting for his state examinations. Godfrey later practiced surgery in the hospital with George Horton, MD, organized the Anatomy Club for the staff physicians and subsequent interns, and made a number of other contributions to Providence Hospital (from the archives of Sisters of Providence and the Providence Medical Center).

At the time of the publication of the first internship list, there were no national standards for internships or, for that matter, for hospitals.[9] Soon after its founding in 1913, the American College of Surgeons established that the records of 100 cases should be reviewed for each surgeon applying for membership in the college. It was quickly discovered, however, that neither the physicians nor their hospitals had such records. A very important effort was then made by the Col-

lege that resulted in hospital standardization—better hospital record keeping, the examination of surgical specimens by pathologists, autopsy reports, and the organization of a defined medical staff for each hospital. Later, a staff of interns served to improve the chance that a hospital would be highly accredited.[9]

Soon after the beginning of hospital standardization, another important change occurred in Washington. The state required an internship for licensure to practice medicine, one of the early states to do so. The records of the Executive Medical Staff of Seattle's Providence Hospital reveal much about the dynamics of the changes that followed. The first meeting of the executive committee of the medical staff was held May 19, 1920. At that meeting, Dr George Horton served as chair and Homer Dudley, MD, was elected secretary. Attending this meeting also was Sister John Gabriel on behalf of the Sisters of Providence, who had stimulated the organization of the medical staff so that the hospital would be accredited. At the original meeting, it was decided that medical records could not contain sealed information, that the name of the surgeon should not appear on requests for reports on pathology specimens, and that the operating surgeon would have authority over how specimens removed at operation would be displayed in the hospital. At their second meeting, it was deemed desirable to exclude some physicians from having hospital privileges at Providence, but action on this matter was deferred on advice from the hospital lawyer.

Early in the fall of 1920, discussions began about the privileges and duties of interns, who apparently were wanted more by the Sisters than by the medical staff. A committee was appointed to consider the matter but deliberated slowly. Sister Gabriel pushed for developing the internship program but little happened. The physicians said that the hospital was not prepared to appoint enough interns to assist them adequately; there were concerns also that the quality of the persons who could be attracted would not be satisfactory. In January 1921 Sister Superior announced that the rules and regulations governing internships at Providence, which were formulated by a committee consisting of Drs Dudley, Allen, and Dowling, were satisfactory to the hospital management, but no action was taken by the medical executive committee. At the May 1921 meeting, the Sister Superior again brought up the subject of internships, but action by the executive committee was again deferred. Interestingly, to the end of the first volume of medical staff notes in 1922, there is no record of the executive medical staff committing itself to support an internship program, although many other notes were made, including a record of appreciation to the Sisters for providing cigars for their meetings.

Sister Gabriel was also involved on behalf of the Sisters of Providence in the organization of the medical staff of the Sacred Heart Hospital in Spokane.[7] Their first organizational meeting was held on August 28, 1919; all licensed physicians of the city and county were invited to this meeting. Although Sacred Heart had appointed four interns "from Eastern schools" in July of 1920, they apparently did not perform satisfactorily and further recruitment was tabled. When the hospital reported to the American College of Surgeons Committee on Hospital Standardization in 1922, it indicated that it lacked interns due to its inability to procure them. The hospital administration, however, persisted in its efforts to secure interns, stimulated by the accreditation visits from the American College of Surgeons. In 1929 the director of the College indicated in a letter to the hospital that interns "would be of great help in promoting better case records as well as increasing the general efficiency of the hospital." Finally in 1931, with approval of the medical executive committee and the persistent work of Sister Mary Alice, an internship program was started.[7]

Growth and Problems for Early Internship Programs

In Seattle, King County Hospital (Harborview) apparently had interns from before 1914, but no records of the program before the 1920s are currently available. The 1921 financial records of the hospital indicate that interns were paid $30 a month; their salaries were increased to $50 a month in 1924—about two thirds the salary of a hospital orderly. Seattle General Hospital was the major site for early graduate medical education in the area; it had 22 interns before 1920. Swedish Hospital Medical Center, which opened in 1910, began its internship program in the 1920s and trained 30 interns in the 1920s and 70 in the 1930s.

Because there were so few Western medical schools—many of the early proprietary schools closed following the Flexner Report—hospitals depended on connections with Eastern schools to try to recruit interns. This situation is illustrated well by recruitment efforts of Virginia Mason Hospital, Seattle, which had opened in 1920. It had a strong link with the medical school of the University of Virginia (Charlottesville) from which its founder, Tate Mason, MD, had graduated.[10] An essay entitled "Reflections," written by A. Stephens Graham, MD, one of Virginia Mason's first two interns, illustrates the uncertainty many Eastern medical school graduates had about coming West and what they found on their arrival.

> My most cherished honor was the appointment by the Dean of the Medical School (University of Virginia) along with Julian Coleman as the first interns of the Virginia Mason Hospital. Actually, however, acceptance was somewhat of a gamble. On New Year's Eve in 1924, in New York City, when I accepted the appointment, I had just been told that morning I had been appointed one of eight interns for St Lukes Hospital, one of the most sought after internships in the country, but I was ranked number eight and missed out on one of the four surgical places leading to a residency. While still bewildered and uncertain, I received a call from a classmate urging me to accept the appointment in Seattle. In my frustrated state, I accepted it and have never regretted it. I was met at the station on July 3, 1925. A quick trip to the Mason Clinic and thence around the lake (Lake Washington) to the summer home of Dr Mason and distinguished friends constituting one large open house for three glorious days. I became acquainted with the men of the staff and their families, as well as leading citizens, including one on his way to becoming the world's greatest producer of planes (Boeing) who continued to be friendly throughout our entire stay.
>
> It is incomprehensible in a city of 340,000, Virginia Mason Hospital has never had an intern, and the remaining three or four hospitals have had extremely few for a city so large. The doctors of the staff were at a loss as to how to use us. We made certain suggestions and explained that we were trained to perform and could carry out lab studies on nights and weekends, including blood chemistries, X-rays, give nitrous oxide, ether, perform spinals, transfusions, undertake deliveries, and were avid performers of autopsies. Amazed, yet delighted, they could avoid the expense of technicians nights and weekends.[11]

In addition to these hospitals, St Luke's Hospital in Spokane and St Elizabeth's Hospital in Yakima also began internship programs in the 1920s, as did the St Alphonsus Hospital in Boise, Idaho.[12] There were also internship programs in the early 1920s in Montana at St Anne's Hospital in Anaconda/Deer Lodge, at the Murray and St James Hospitals in Butte, and in Glendive and Missoula. All of these sites were along the railroad line, and it was apparently hoped that more physi-

cians would be attracted to the area through the offer of internship positions.

By 1924 there was enough growth in the number of internships in the country and enough shrinkage in the supply of medical graduates, halving between 1905 and 1920, that there was an internship available for every medical graduate. The expansion in the number of hospitals offering internships and the total number of positions available continued, however. In Washington there were additional positions in Bremerton, Ft Stillacoom, Longview, and in Tacoma at the Pierce County and Tacoma General Hospitals.[13]

As new positions were opened, more internship vacancies occurred. To counter this problem, hospitals lengthened the internship program, often making 1½- to 2-year appointments. They also sometimes added amenities to attract interns. For instance the Providence Hospital began paying 6% interest on the deposits required from interns when they accepted positions. Hospitals also began to accept foreign medical graduates to fill their increasing vacancies.

Specialization and Residency Programs

Another important trend of the 1920s and 1930s influencing the early Northwest general medical education programs was the rise in specialization. The first specialty boards were the American Board of Ophthalmology (1917) and the American Board of Otolaryngology (1924), followed by the formation of many others over the subsequent decade. Although there was then an ample supply of general physicians in the country, relatively few had had multiple years of graduate medical education. In Washington by the 1930s, there were many internships but almost no advanced training. For instance, in 1934 there were nearly 2,400 residency (postinternship) positions in the US, but there was only one residency position in Washington and none in her sister states of Alaska, Montana, and Idaho.[14] In 1939 there were nearly 4,600 hospital-based postinternship positions in the US (assistant residencies, residencies, and fellowships), but only 13 of these positions were in Washington.[15] By 1944, the year before the University of Washington School of Medicine was started, there were 79 graduate medical education positions (59 internships and 20 residency positions) in Washington (77) and Montana (2). Until 1950, all of the medical school graduates and almost all of the medical specialists who practiced in Washington were trained elsewhere.

Beginning a Medical School

Ideas and plans for the beginning of a medical school at the University of Washington date from the 1880s.[2] Although there were several abortive efforts to begin a medical school before World War II, little happened. In the 1940s, however, physicians of the area, particularly those already involved in graduate medical education, and a cluster of interested basic scientists at the university successfully fostered the idea of beginning a school. David Matheny, MD, a Seattle surgeon who served as Chief of Staff and as an active teacher of the interns and residents at King County Hospital, Dr Homer Dudley, who had served on the committee to begin the internship program at Providence, and Alfred Strauss, MD, a prominent alumnus of the University of Washington, who practiced then in Chicago, all were influential in the beginnings of the school. After the recruitment of Ed Turner, MD, as the school's first dean, Dudley and Edwin Bennett, MD, then General Superintendent at Harborview, supported establishing Harborview-based graduate medical education programs under the auspices of the university. Dean Turner also then provided support for the establishment of the surgical residency at Virginia Mason (from the University of Washington School of Medicine Archives).

In the 1950s and 1960s, after the recruitment of clinical department heads to the university, specialty and subspecialty programs flourished, both at the university and at the teaching hospitals of the region. For instance, according to their Office of Medical Education records, the Swedish Hospital Medical Center developed programs in radiation therapy, anesthesiology, pathology, general surgery, obstetrics and gynecology, and diagnostic radiology. The prevailing ideas of this era were that most medical problems could be dealt with better by specialists than generalists. By the mid-1960s, however, it was recognized that there was a growing need for more and better trained generalists and for new approaches to address the need for good physicians for the small towns and rural areas of the region. The reduction of the number of medical schools in the country in the early part of the century and the aging of the nation's general practitioners, coupled with advancing specialization, had created this problem.

A Regional Graduate Medical Education Program

To this point in time, it can be fairly concluded that Seattle and the Northwest had largely played "catch up" in developing medical education and graduate medical education programs. There had been a steady growth in the size and quality of the education and research programs at the university. The attractiveness of the Pacific Northwest had helped to keep many of the outstanding medical school graduates and faculty who were recruited. Although there were some difficult times surrounding the opening of University Hospital, good relationships were steadily developed between the school, hospitals in the Seattle community, and physicians of the region.

It was with the development of regional programs for training generalists in family practice, internal medicine, and pediatrics, and with the beginning of the school's WAMI (Washington, Alaska, Montana, Idaho) program in the late 1960s and early 1970s that the special character of its present graduate medical education program was established nationally. In 1971 a family practice residency network was begun with sites for training in Seattle, Tacoma, Bremerton, Yakima, Spokane, and Boise, with links to many smaller communities. The network was molded substantially from the resources that were set aside early in the century by community hospitals for internship training. Similarly, cooperative agreements were established for expanded numbers of training positions in internal medicine using several hospitals in the Seattle area (University, Harborview, US Public Health Service, Seattle Veterans Administration, Swedish, and Providence hospitals), as well as at sites as far away as Boise, Idaho; Billings, Montana; and Fairbanks, Alaska. The training program in general pediatrics also linked training at the Seattle Children's Hospital and Medical Center with many other sites in the region. Concomitant with these changes, small programs in several specialties were discontinued as part of an overall effort of the school and hospitals to more closely match the graduate medical education efforts in the region to the need for physicians in various specialties. The leadership of Jim Haviland, MD, who came to Seattle in

1940 and served as an early Assistant Dean, Associate Dean, and Acting Dean of the school while maintaining a part-time practice, are particularly noteworthy. He led in developing the contractual arrangements that brought the teaching hospitals and the School of Medicine together in an effective working arrangement. As a result, now 77% of the civilian general medical education positions of the four-state region are centrally coordinated through the school of medicine.[16]

Recently a number of commissions and reports have addressed national problems with the organization and management of general medical education in our country. The principal concerns are the costs, content, and oversight of these educational programs, which nationally now involve 75,000 young physicians and cost almost $3 billion annually. For the four states of Washington, Alaska, Montana, and Idaho, there are now 888 interns and residents in training (including military programs), just over 1% of the national total. Nearly 60% of these residents are completing training in the fields of family medicine, internal medicine, and pediatrics.[14] There are still fewer residency positions, as well as fewer medical student positions, per capita or per hospital bed, than in most other areas of the country, but, by contrast with a half century ago or even more recently, the quality is now perceived to be good, and the demand is continually increasing.

This history of graduate medical education ties together the beginnings of Northwest hospitals and their internship programs and the beginning of the University of Washington School of Medicine. It illustrates how a spirit of cooperation, partially in response to geographic isolation, has served steadily to strengthen medical education in this region. Within this history are many individual stories of the coming West of young physicians who have served the Northwest with distinction. It is a history to which many have contributed and a development from which many more have benefited.

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Public Health and Preventive Medicine

Mortality From Unintentional Injuries in California, 1985

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This is one of a series of articles from western public health departments.

In 1985 unintentional injuries were the fourth leading cause of death among California residents, causing 10,380 deaths. They were the leading cause of potential life lost, accounting for 278,109 years lost. This was more than twice the number of years lost due to heart disease and 1½ times the number lost due to cancer. Motor vehicle traffic accidents were the leading cause of unintentional injury deaths, accounting for half (5,158) the deaths. The next two leading causes were poisoning (especially for men aged 25 to 44 years) and falls (especially among persons aged 75 and older). Drowning was second to motor vehicle accidents as a cause of death in children aged 1 to 14 years. California's age-adjusted injury mortality rates in 1985 were lower in coastal and urban counties than in inland and rural counties, and these rates were generally lower in counties having organized systems of trauma care.

(Saunders LD, Green M, Doebbert G, et al: Mortality from unintentional injuries in California, 1985. West J Med 1989 Apr; 150:478-483)

Unintentional injuries were the fourth leading cause of death in the United States in 1984, being surpassed only by heart disease, cancer, and cerebrovascular disease. Almost 93,000 Americans died of unintentional injuries in 1984. Of these, half were due to motor vehicle accidents.[1] Unintentional injuries resulted in 2.3 million years of potential life lost in the US in 1984, greater than from any other cause.[2]

Most studies of unintentional injuries as a whole are based on national data, and a recent report from the federal Centers for Disease Control stresses the need for more local definition of injury problems so that injury control measures can be designed and targeted to address the priorities present at the state and local levels.[3] The report also points out that death certificates are an accessible source of injury mortality data and that, with population data, injury death rates can be calculated for local areas. We undertook this study to assess the relative importance of unintentional injuries as a cause of death in California and to determine the epidemiology of specific types of injuries in the state.

Methods and Materials

Death certificates for 1985, the most recent year for which complete data were available, were examined for all deaths occurring in the state of California. Causes of death were categorized in accordance with the methods used by the Centers for Disease Control for national data collection,[2] modified to allow comparison with data published annually for California (Table 1).[4] Data from the 1985 Deaths Statistical Master File maintained by the California Department of Health Services were used for injury figures. Population data were provided by the California Department of Finance.

The relative importance of unintentional injuries was determined by comparing the total number of deaths, the total number of years of expected life lost based on the life expectancy remaining at the time of death,[5] and the total number of years of potential life lost before age 65 years.

The relative importance of the different categories of unintentional injury in California was also determined. Categories used by the Centers for Disease Control for unintentional injuries (Table 2) were modified to allow comparison with data previously published for California.[6]

The total number of deaths was used to compare the importance of different unintentional injury categories for specific age-sex groups. Mortality rates for specific causes of injury death were plotted by age group for each sex.

Results

As was the case nationally in 1984, unintentional injuries were the fourth leading cause of death among California residents in 1985, following heart disease, cancer, and cerebrovascular disease. In this year, unintentional injuries were responsible for 10,380 California deaths (5.1% of all deaths) or 28 deaths per day on the average. When combined with deaths from homicide and suicide, there was a total of 46 deaths per day, on the average, due to trauma.

Unintentional injuries were the third leading cause of years of expected life lost for California residents in 1985,

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TABLE 1.—*Leading Causes of Death in California for 1985: Number, Years of Expected Life Lost (YELL), Years of Potential Life Lost Before Age 65 Years (YPLL), and Average Number of Deaths per Day*

Cause of Death	ICD Codes	Residents of California			Deaths per Day, No.
		Number	YELL*	YPLL†	
Diseases of the heart	390, 398, 402, 404-429	69,046	926,346	133,091	189
Malignant neoplasms	140-208	45,615	823,694	187,014	125
Cerebrovascular disease	430-438	15,222	180,944	23,759	42
Unintentional injuries	800-949	10,380	425,425	278,109	28
Chronic obstructive pulmonary disease and allied conditions	490-496	8,606	120,010	12,947	24
Pneumonia and influenza	480-487	8,046	94,838	17,160	22
Chronic liver disease and cirrhosis	571	3,965	100,799	38,130	11
Suicide	950-959	3,782	138,932	82,414	10
Diabetes mellitus	250	2,997	48,797	10,401	8
Homicide	960-969	2,818	130,879	89,321	8
Certain conditions originating in the perinatal period	760-779	1,992	150,393	128,354	5
Congenital anomalies	740-759	1,598	104,197	84,883	4
Acquired immunodeficiency syndrome	279.1	1,190	47,603	29,317	3
Sudden infant death syndrome	798	688	51,977	44,361	2

ICD=*Manual of the International Classification of Diseases, Injuries, and Causes of Death*, 9th Revision, World Health Organization, 1975

*Years of life lost based on life expectancy remaining at time of death.
†Years of life lost before age 65.

TABLE 2.—*Cause of Injury Groups**

Cause	ICD Codes
Motor vehicle traffic injuries	E810-E819
Motor vehicle nontraffic injuries	E820-E825
Other transport injuries	E800-E807, E826-E848
Unintentional poisoning	E850-E869
Unintentional injuries due to falls	E880-E888
Unintentional injuries caused by fires and flames	E890-E899
Unintentional drowning	E910
Unintentional injuries due to choking	E911-E913
Other, unintentional injuries	E900-E928†
Misadventures and adverse effects	E870-E879, E930-E949

*From the World Health Organization, *Manual of the International Classification of Diseases, Injuries, and Causes of Death* (ICD), 9th Revision, 1975.
†Excluding code E910 to E913.

resulting in a total of 425,425 years lost. This was exceeded only by the years of expected life lost from heart disease (926,346) and from cancer (823,694) deaths. For years of potential life lost before age 65 years, unintentional injuries ranked as the number one cause of death, being responsible for 278,109 potential years lost in 1985. This was more than twice the 133,091 potential years lost because of heart disease deaths and 1½ times the 187,014 years lost because of cancer deaths.

Motor vehicle traffic accidents (MVTs) were the leading cause of unintentional injury deaths in 1985, accounting for 5,158 (49.7%) of all injury deaths. Of the 5,158 deaths, 3,670 were to males. Motor vehicle traffic accidents accounted for approximately half of all unintentional injury deaths to both male and female victims (Figure 1).

The greatest number of MVT deaths involved drivers (1,716 or 33.3%), with pedestrians and passengers accounting for 17% and 18%, respectively. The number of motorcycle driver deaths was 573, or 11% of the total. Bicyclist deaths totaled 139 or 3% of the total (Figure 2).

Poisonings and falls caused more than 1,000 deaths each in 1985 (1,425 and 1,126, respectively). Of the 1,425 poisoning deaths, 1,088 (76%) were male victims, and 655 (58%) of the 1,126 deaths from falls involved males. Altogether, MVTs, poisonings, and falls caused 7,709 (74%) injury deaths.

After motor vehicle traffic accidents, poisonings, and falls, the number of deaths resulting from any one type of injury declined sharply. Drowning, the fourth leading cause of injury-related death, was responsible for 521 deaths in 1985. Following this were choking (378 deaths or 3.6%), other transport (352 deaths or 3.4%), fire and flames (328 deaths or 3.2%), and misadventures and adverse effects of surgical and medical procedures (233 deaths or 2.2%). There were 721 deaths from all other unintentional injury causes, which included injuries due to natural and environmental factors and those due to falling objects, machinery, guns, explosive material, and domestic wiring and appliances.

Injury Mortality Rates—Sex and Age Patterns

For all unintentional injuries, male mortality rates drop from the 1- to 4-year age group through the 10- to 14-year age group, rise rapidly from ages 15 through 24, decline gradually to the 50- to 54-year age group, then start to rise with a steep ascent after 70 to 74 years. Female rates are lower than male rates in all age groups, particularly for ages 15 to 44 and older than 85, but follow the same general age pattern (Figure 3).

Mortality rates for motor vehicle accidents were higher for male than for female victims in all age groups. For example, in the 20- to 24-year age group, the male mortality rate of 62.2 deaths per 100,000 persons was almost four times the female rate of 16.9 per 100,000. For both sexes, the graphs are bimodal (Figure 4), with peaks for males at ages 20 to 24 and 85 years and older and peaks for females at 15 to 19 and 80 to 84 years.

Mortality rates from unintentional poisoning were higher for men than for women younger than 65 years (Figure 5). In the 30- to 34-year age group, the male rate of 24.2 per 100,000 was almost five times the female rate of 5.3. There was a steep rise in mortality rates among males from 1.6 deaths per 100,000 at 15 to 19 years to a peak of 24.2 deaths per 100,000 at 30 to 34 years, after which the rates fell

Figure 1.—The graph shows the number of deaths to California residents from unintentional injuries, male **(black shading)** and female **(white shading)**, for the year 1985. MVT = motor vehicle traffic, MVNT = motor vehicle nontraffic

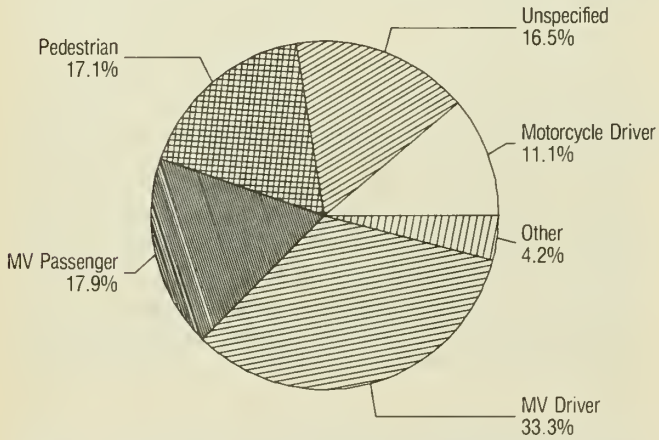

Figure 2.—The pie chart shows the percentage of motor vehicle (MV) traffic accidents by category of victim in California in 1985.

rapidly through ages 70 to 74 before reaching a secondary peak at ages 80 to 84.

For all age groups, male mortality rates from unintentional falls were higher than those for females (Figure 6). Rates for both men and women rose steeply after age 65. The mortality rate for men aged 75 to 79 was 26.4 per 100,000. The rate then jumped to 61.3 for men aged 80 to 84 and to 169.7 for men aged 85 and older. The mortality rate for women aged 75 to 79 was 14.9 per 100,000, which increased to 44.1 for women in the 80- to 84-year age group and reached 103.8 for women aged 85 and older.

Drowning mortality rates tended to be higher for male than for female victims at all ages except infancy and 75 to 79 years (Figure 7). For both males and females, rates peaked in the 1- to 4-year and the 85 years and older age groups. The rate for boys aged 1 to 4 years was 7.7 per 100,000 while for girls it was 5.0 per 100,000. The rate for men aged 85 and older was 7.1 per 100,000, but for women it was 2.7 per 100,000.

Mortality rates from unintentional choking tended to be higher for males than for females at all ages except infancy (Figure 8). The highest rates occurred at the extremities of life. For children younger than 1 year, the rate for males was 8.4 deaths per 100,000 and for females 8.8 per 100,000. For persons aged 85 and older, the male rate was 22.6 and the female rate 13.7 per 100,000.

Unintentional Injury Mortality Rates—Variation by County

Age-adjusted unintentional injury mortality rates for California's 58 counties are shown in Figure 9. The overall state injury mortality rate in 1985 was 39.2 deaths per 100,000 population. The county rates ranged from a low of 30.4 to a high of 98.8 deaths per 100,000. In general, coastal and urban counties had lower mortality rates than inland and rural counties.

Injury mortality rates were generally lower in the 13 counties having formally organized systems of trauma care.* The overall rate in these counties was 37.2 per 100,000 population. The overall rate in the remaining 45 counties was 46.5 per 100,000 population. Trauma care systems were usually found in the state's most populous urban and coastal counties.

Discussion

The results of this study leave little doubt that unintentional injuries are a serious public health concern for California. They further identify the major causes of injury deaths and the high-risk population groups by injury type.

Successful prevention programs target their efforts. They deal with a specific injury type for a specific population using a specific intervention.[7] For instance, for motor vehicle traffic accidents, the leading cause of injury deaths, the use of seat belts has proved to be an effective preventive device. Mortality rates for motor vehicle traffic injuries rose from 21.2 per 100,000 in 1976 to 24.9 in 1979, then decreased each year to 18.7 in 1983 before rising to 20.3 in 1984 and declining again to 19.6 in 1985 (Figure 10). Definitive infor-

*Alameda, Contra Costa, Fresno, Los Angeles, Napa, Orange, Riverside, Sacramento, San Bernardino, San Diego, San Francisco, Santa Clara, and Tulare counties.

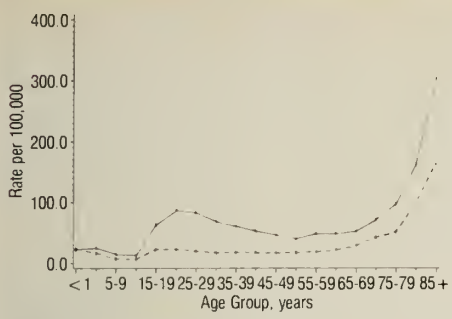

Figure 3.—The graph shows mortality rates from all unintentional injuries, by sex and age, in California in 1985. Female rates are indicated by the dashed line and male rates by the solid line.

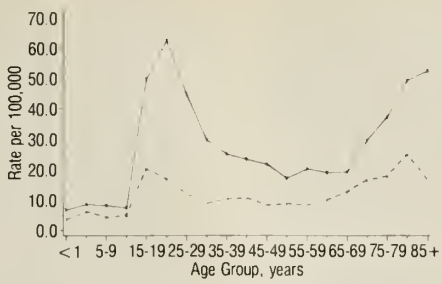

Figure 4.—The graph shows mortality rates from motor vehicle traffic accidents, by sex and age, in California in 1985. Female rates are indicated by the dashed line and male rates by the solid line.

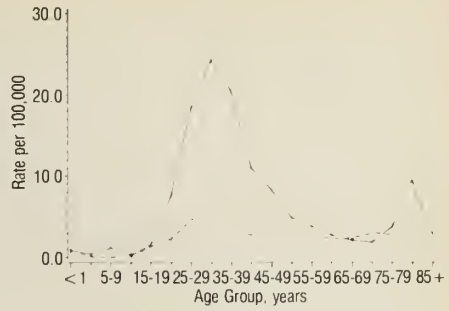

Figure 5.—The graph shows mortality rates from poisoning, by sex and age, in California in 1985. Female rates are indicated by the dashed line and male rates by the solid line.

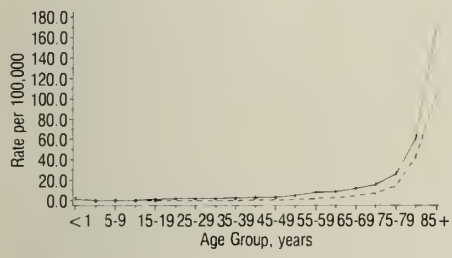

Figure 6.—The graph shows mortality rates from falls, by sex and age, in California in 1985. Female rates are indicated by the dashed line and male rates by the solid line.

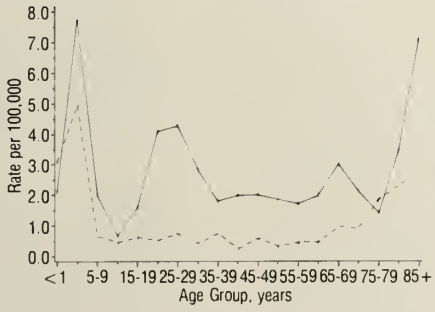

Figure 7.—The graph shows mortality rates from drowning, by sex and age, in California in 1985. Female rates are indicated by the dashed line and male rates by the solid line.

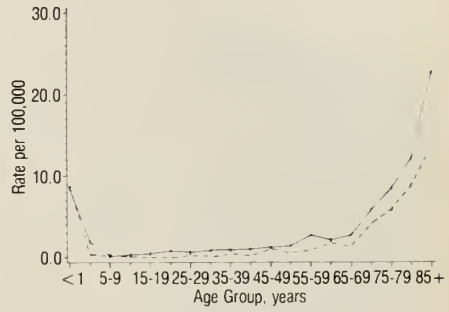

Figure 8.—The graph shows mortality rates from choking, by sex and age, in California in 1985. Female rates are indicated by the dashed line and male rates by the solid line.

mation about the effect of California's mandatory seat-belt-use law that became effective January 1, 1986, is not yet available; preliminary indications are that this law is decreasing MVT-related morbidity and mortality. This would be consistent with other studies that have shown the effectiveness of mandatory seat-belt-use laws in other states. In New York, for example, the reduction in fatalities during the first nine months was 9%.[8] A North Carolina study found that the use of seat belts reduced the risk of serious injury to the driver by 58% and the risk of fatal injury by 73%.[9]

The use of passenger restraints for young children is also an effective injury control device. Effective January 1, 1983, California law required that children younger than 4 years or weighing less than 18 kg (40 lb) be transported in a passenger-restraint system. After a year, an 8.4% reduction in MVA-related childhood injuries was found.[10]

The use of helmets reduces the severity of head injuries for both motorcyclists and bicyclists. Various studies have found that laws requiring helmet use reduce motorcyclist deaths by 30%. States that revoked their helmet use laws after a 1976 change in federal requirements experienced a substantial drop in helmet use and a 40% increase in the number of deaths.[11] Similarly, a study of bicyclist deaths in Dade County, Florida, concluded that because the head or neck is most seriously injured in five out of six bicyclist deaths, helmet use would greatly reduce the number of fatalities.[12]

Numerous studies have shown that drinking alcoholic beverages is a factor in more than half of fatal motor vehicle accidents. A study from Illinois and Michigan found a significant immediate reduction in the number of fatalities among drivers aged 21 years and younger after these states raised their minimum drinking age.[13] The estimated annual cost of alcohol-related motor vehicle accidents nationally is about $12 billion.[14]

Teenagers and young adults, especially young men, are most at risk for motor vehicle, motorcycle, and bicycle accidents. Enforcement and education programs regarding the use of seat belts and helmets and refraining from drinking and driving can be effectively directed to these groups. Physician support of these programs is critical to their success in reducing injuries. For instance, physicians can reinforce these programs by encouraging patients they see for physical examinations, and during other visits by teenagers and young men, to participate in these programs. Likewise, pediatricians and family physicians can put a greater emphasis on educating parents as to the importance of correct child-safety-seat use. The total annual cost of motor vehicle crashes nationally is estimated to be about $70 billion.[15] It is reasonable to estimate the cost in California at 10% of the national figure, or about $7 billion.

The group at the highest risk from unintentional poisoning deaths are young men, ages 25 to 44. Information from death certificates indicated that most of these poisoning deaths were due to heroin and cocaine use. Other studies confirm an increased use of these drugs in recent years. For example, one study found that after the epidemics of heroin abuse in the United States during the mid-1960s and the mid-1970s, another occurred during the early 1980s.[16] The availability of "black tar" heroin, purportedly of high purity and low price, may be responsible for recent increases in heroin morbidity and mortality.

Reducing the number of unintentional poisoning deaths depends to a large extent on the success of anti-drug use

programs. In the *Bulletin on Narcotics* of the United Nations, such programs are reported to be most successful when selected in response to the perceived needs of target groups such as parents, students, teachers, workers, and persons dealing with youth problems.[17] As with alcohol prevention programs, physician support of anti-drug use efforts is invaluable. Physician reinforcement efforts should be focused particularly in their contacts with young adult male patients. Also, it is crucial that female patients understand the harmful effects of alcohol and drug use during pregnancy.

One of the most effective means of reducing drowning deaths among children, the group at highest risk, is installing childproof fencing around residential swimming pools. A study of drownings in Sacramento County found that children younger than 5 years accounted for 35% of all drownings during the period 1974 to 1984.[18] Additional findings were that a third of all drownings and 58% of drownings among children through 4 years of age occurred in swimming pools and that 80% of children appeared to have gained access to the pool directly from the house or yard. Similarly, an Australian study found that the drowning rate in a community where childproof fences were required around home swimming pools was a ninth the rate in a comparable community where such fences were not required.[19]

Figure 9.—The map shows age-adjusted mortality rates from unintentional injuries to California residents by county for the year 1985.

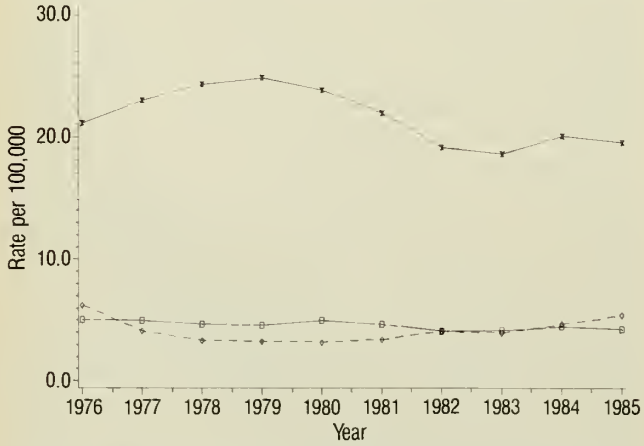

Figure 10.—The graph shows the trends of mortality rates from motor vehicle traffic accidents (∗), poisoning (◇), and falls (□) in California, 1976 through 1985.

The Sacramento study found that survival following an immersion incident critically depends on the rapidity with which effective emergency medical care is received. Too often a child received no resuscitation care until emergency medical service personnel arrived. Communitywide training in cardiopulmonary resuscitation, targeting families with small children and residential pool owners, might substantially improve postimmersion survival rates.[18]

The public health importance of drowning prevention is underscored by the costs associated with caring for near-drowning victims. Over the three-year period 1984 through 1986 at a major children's hospital in Orange County, California, eight critical near-drowning patients having a total of 422 days of hospital care accrued charges of $631,000.[20] The average cost for acute care in hospital for a near-drowning victim in Orange County was $1,650 per day. To maintain patients at two California State Developmental Centers in Orange County, at an average cost of care of $225 per patient day, the yearly total cost of care to the state of California was more than $3 million. Home care cost for near-drowning victims, with parents rendering primary service, is estimated at $8,000 to $10,000 per month.

California residents aged 65 and older, and particularly those 75 years and older, are at the highest risk of death from both falls and choking. Nationally about 1,800 fatal falls and 200 fatal choking incidents occur each year in long-term-care residential institutions such as nursing homes and extended care facilities.[11] Incidents of fatal falls and, to a lesser extent, deaths from choking also are on record as occurring in California nursing homes. Prevention efforts could be targeted to these institutions and to those who care for the elderly in other settings, including the home. Physicians and other health care personnel need to be knowledgeable about emergency airway management to prevent choking fatalities.

Three quarters of all deaths from fire and burns result from house fires, with death rates being highest among young children and the elderly. About 79% of residential fires occur between 8 PM and 8 AM, with 40% between 12 AM and 4 AM. Smoke alarms to give early warning of fires are an effective preventive device.[21] Primary care physicians could be more knowledgeable about smoke alarms and might routinely encourage patients to properly install and maintain home alarms. These efforts should be especially directed toward the elderly, who are most at risk of fire injuries and deaths.

Cigarettes are the leading cause of fatal house fires, about half of which are started by smoldering cigarettes that ignite upholstered furniture or mattresses. Heating equipment is the second leading ignition source. Prevention measures include reducing the ignition potential of cigarettes and heating and electrical equipment and reducing the flammability of materials and the toxicity of their combustion products.[11]

Our study also shows that unintentional injury mortality rates were generally lower in California's urban and coastal counties, locations where organized systems of trauma care

usually were found. Although data measuring the effectiveness of individual county trauma care systems in California have not been widely reported, available evidence indicates that organized trauma care systems notably reduce unintentional injury mortality. For instance, San Diego County data show a 36% reduction in the proportion of deaths to total injuries after its trauma care system was established, going from 26.4% in the three months before implementing its trauma system to 19.3% in the first year of the system's operation.[22] There was also a reduction in the proportion of preventable deaths from 13.6% to 2.4% and a further 33% reduction in the number of preventable deaths from the first to the second year of the operation of the trauma system. Data from Orange County also indicate a decrease in the proportion of deaths to injuries, before and after implementing a formal trauma system, declining from 22% during 1980 and 1981 to 8% during 1985 and 1986.[23]

In summary, this review of the epidemiology of unintentional injuries in California underscores the importance of trauma as a public health concern in this state and the need, as well as efficacy, of targeted interventions to reduce the morbidity and mortality of these conditions.

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Commentary

A Tangled Love Affair

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

I am being courted—openly and brazenly. I have been showered with gifts. I have been invited out to breakfast, lunch, and dinner. Each day I am deluged with mash notes of various sizes, shapes, and colors.

It is I, the average American physician, whose favors are being so eagerly sought. The suitor: the American pharmaceutical industry.

Here is a partial list of my proferred gifts: pens, flashlights, paperweights by the dozen. Baseball caps and umbrellas. Fancy wood puzzles and shiny plastic games for my grandchildren. Automatic light switches, night lights, and electronic gadgets. Blankets, T-shirts, windbreakers.

I have been invited to continuing medical education meetings held in conjunction with steak and eggs for breakfast, crab Louie for lunch, and gourmet dinners at the newest and poshest restaurants. Recently, I was even offered a $100 honorarium if I would attend a dinner meeting where I would listen to a sales pitch for a certain cholesterol-lowering product.

Each day I receive seven or eight pieces of personalized mail, some of it offering gifts ranging in value from 80 cents to $8 each. Most of these mailings contain a request for a signature indicating that: Yes, I do love you and your product—please keep your mail (and your gifts) coming.

Why is all this happening? Why is the American physician being sought after so seductively—and expensively? An article recently published in *Medical Advertising News* gives me a clue as to just how and why this is being done. Physicians are still the only ones who can prescribe the pharmaceutical industry's brand name drugs. This article gave practical suggestions on how a physician can be charmed into writing prescriptions for their products.

American physicians can be standoffish, wary of the "hard sell," and before one can use the soft sell, you must first get their attention. The article advised how this could be accomplished: Make the mailing colorful, dimensional. Put it in a box or a tube, or even in a plain brown envelope—personalized, of course. Be creative. Be sure to enclose a card that promises samples or another trinket.

It is estimated that the drug industry spends $55 million a year on direct mail advertising. That apparently exceeds the amount spent on direct professional promotion, including those helpful office visits by medical representatives.

It occurs to me that someone must be paying this bill. I come to the disturbing conclusion that it's not the advertising agency nor the pharmaceutical house. Obviously, it's my patient who picks up the tab when I'm wined and dined and given trinkets and gadgets.

My guilt deepens. Could this also be one of the reasons why the cost of oral contraceptives has risen from $2.50 a month to $13.00? Or why an NSAID capsule can cost $1.25? Must I, the besieged American physician, therefore accept the blame for the high cost of prescription drugs?

I protest, insisting that I am the victim of circumstances, a victim of the marketing of medicine. Of fierce competition in the drug industry resulting in the introduction of yet another me-too, anti-inflammatory medication or a clone antihypertension pill as each month rolls by.

In my protest I am joined by my pharmacist friend down at the corner drug store. He, too, is unhappy with those high prices. We both cringe when each day we hear an outraged patient say, "Do you know how much they charged me for that pill you prescribed for me? Fifty-five bucks! No wonder you guys are rolling in it."

We know it would be futile to try to explain how many years of research went into the production of that "pill." Or how many millions of dollars a drug company must invest in order to comply with the Food and Drug Administration's rigid requirements.

My patient also may be hard to convince when I tell him the generic story of how these off-brand companies have been able to bypass the FDA's strict efficacy regulations, accepting a free ride on the coattails of the brand name company's research efforts.

Is there a solution? It may be that the American physician, certainly this physician, is ready for a change. I cannot help but wonder if it's time to ask my suitors to cool their ardor. I'd say to my pharmaceutical friends: You can and should keep on supplying me with good educational information, but steak and eggs for breakfast is a bit too much. It would be nice if some of those dollars could be funnelled back into my patients' pockets. Why not plan to put more into purely educational programs here at home? We physicians do attend continuing medical education meetings. We do read periodicals. We do listen to tapes.

One more thing. It has been rumored that you are toying with the idea of reducing your expenditures by cutting down on the use of medical representatives. Don't, I beg of you! Even though I may not always be ready to admit it, these people are a source of valuable, practical information. And I have noticed that, while a gadget or a trinket may be quickly forgotten or discarded, I will invariably prescribe the medication that has been described and sampled to me by your capable, soft-sell representative.

Oh, sure, I hope you'll keep on courting me, but why not skip the chocolates and the roses?

(Fox ERW: A tangled love affair. West J Med 1989 Apr; 150:484)

Dr Fox is in private practice in Coeur d'Alene and is the Special Editor for Idaho.
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CONTINUING MEDICAL EDUCATION

(Continued from Page 413)

July 14—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 31-August 3—**Practical Orthopaedic Sports Medicine.** Children's Hospital Oakland at Hyatt Regency, Waikoloa, Kona Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Stuart Zeman, MD, 2999 Regent St, No 203, Berkeley 94705. (415) 540-8686.

August 11-12—**Office Practice Enhancement: Non-invasive Diagnostic Testing.** Medical Education Collaborative at Lake Tahoe, Nevada. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 8-9—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Napa. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 13-15—**Primary Care Medicine: Principles and Practice.** UCSF at The Portman, San Francisco. Wed-Fri. 20 hrs. $385. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

IDAHO

May 7-10—**Idaho Academy of Family Physicians—Annual Meeting.** Coeur d'Alene Convention Center. Sun-Wed. Contact: Irma Sparks, Exec Dir, Idaho Academy of Family Physicians, PO Box 175, Boise 83701. (208) 362-4808.

July 27-29—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701.

August 7-8—**Northwest Regional Perinatal Conference—Current Issues in OB/GYN, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Mon-Tues. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 11-13—**New Mexico Medical Society Annual Meeting—A Celebration of the University of New Mexico School of Medicine's 25th Year.** Holiday Inn Journal Center, Albuquerque. Contact: New Mexico Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 486)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

April 1—**Cytomegalovirus and Herpes Simplex Virus Infections in the Immunocompromised Patients: DX & TX** (Sponsor: UUMC). Sat. University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 4-5—**Ethics and Health: Issues of Autonomy: Conflicts in Decision Making** (Sponsor: UUMC). Thurs-Fri. University of Utah, Salt Lake City. Contact: (801) 581-5809.

May 11-12—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 488)

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Please see next page for brief summary of prescribing information.

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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 487)

June 18-23—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 12-14—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Salt Lake City. Contact: Barbara Saffel, (801) 466-3500.

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon. Jackson Hole, Wyoming. Contact: Midge Beckman, (801) 581-7480.

July 20—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

September 28-29—**Laser Surgery: General Surgery ND: YAG, CO** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

October 12-13—**Laser Surgery: Gastroenterology ND: YAG** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 14-15—**Tacoma Surgical Club.** Fri-Sat. Tacoma. Contact: (206) 627-7137.

April 20-21—**Ergonomics.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

April 22—**AIDS Education.** Spokane. Sat. Contact: UW, (206) 543-3910.

April 26-27—**Computers in Medicine (Clinical Applications).** Tacoma. Wed-Thurs. Contact: (206) 627-7137.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069.

May 17—**Neurology.** Tacoma. Wed. Contact: (206) 627-7137.

May 18-19—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

May 20—**AIDS Education.** Everett. Sat. Contact: UW, (206) 543-3910.

June 1-3—**International Symposium on Pediatric NeuroOncology.** Seattle. Thurs-Sat. Contact: U/W.

June 2—**Current Otology.** Seattle. Fri. Contact: VMMC.

June 26-27—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: (206) 627-7137.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 8-10—**Wyoming Medical Society—Annual Meeting.** Teton Lodge, Jackson. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009.

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Contact: Midge Beckman, (801) 581-7480. ◆

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SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN, Oncologist, or Infectious Disease Specialist at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

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Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, General Internal Medicine, Neurology, General Surgery (breast disease focus), OB/GYN. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Dr Larry W. Hirons, Medical Director
1162 Willamette St
Eugene, OR 97401

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OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294, or 1 (800) 234-1231.

URGENT — FAMILY PRACTICE / GENERAL PRACTICE Physicians needed for excellent solo and group opportunities across the U.S. For information, call (602) 990-8080; or send CV in confidence to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

NORTH IDAHO. Family Physician needed to join four physician group. College and two state universities within the locality. Area provides abundant outdoor recreational opportunities. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee-for-service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

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EUGENE, OREGON. Family Physicians, BE/BC, sought to join growing 36 physician Family Practice/Internal Medicine group in Eugene and nearby rural Cottage Grove. OB optional. Excellent OB support available. Initial income guarantee with incentive. Partnership anticipated after two years. Outstanding schools. Abundant cultural and recreational opportunities. Please send CV or call Rob Daugherty, MD, Oregon Medical Group, 78-A Centennial Loop, Eugene, OR 97401; (503) 688-9140.

CARDIOLOGIST, NONINVASIVE OR INVASIVE. BC/BE to join busy solo Invasive Cardiologist in San Jose, California. Excellent benefits and early partnership opportunity for motivated Cardiologist. Expertise required in echo Doppler, stress testing, Swan-Ganz, and pacemaker insertion. San Jose is located 50 miles south of San Francisco, close to numerous cultural and recreational opportunities. Please send CV to Number 136, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

VENTURA (VENTURA COUNTY). Multispecialty group of 42 physicians has an opening for a BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

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PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

PULMONOLOGIST. Pulmonologist wanted as associate in very busy Pulmonary/Critical Care practice in Kern County, California. Practice is 100 percent Pulmonary/Critical Care and includes pulmonary consultation, pulmonary physiology laboratory, pulmonary rehabilitation, respiratory care, state-of-the-art sleep lab available. Excellent opportunity for BC/BE Pulmonologist looking for potential partnership. Those interested please send CV and inquiries to Dale T. Herriott, MD, Inc, 2525 Eye St, Ste 2B, Bakersfield, CA 93301.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; telephone 1 (800) 544-1987.

BC/BE GENERAL INTERNISTS needed for multispecialty group in Sacramento, California. We are an established Department of Medicine with close university affiliation. Pleasant practice setting where physicians are free to practice the highest quality medicine with full access to diagnostic, therapeutic, and consultative services. Our patients are from a growing Sacramento community with a good cost of living. Our hospital provides a substantial part of University of California Davis residency training program. Excellent in-house continuing medical education program. We are a successful, stable medical group experiencing robust growth. Outstanding starting salary and advancement. Full benefits and retirement. This is a quality career opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, 2025 Morse Ave, Sacramento, CA 95825.

BC/BE INTERNIST. In northern California wine country. Join two man group in private practice of Internal Medicine. Subspecialty interest OK. Reply to Number 138, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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BE/BC Internist. We currently are seeking highly qualified Internists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV:

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Chief, Department of Internal Medicine
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Hayward, CA 94545

PHYSICIANS WANTED

INTERNIST BE/BC to join growing practice in Tacoma, Washington. Practice is oriented to women's health issues. Women encouraged to apply. Send CV to PO Box 2122, Gig Harbor, WA 98335; (206) 858-8686 evenings.

NORTHERN CALIFORNIA. Family Practice opportunity with community health center. Modesto location. Salary plus incentive program. Spanish fluency desirable. Contact Michael Sullivan, Executive Director, Merced Family Health Centers, Inc, PO Box 858, Merced, CA 95341; (209) 383-1848.

SUN VALLEY, IDAHO. Diagnostic Radiologist for mountain resort hospitals needed to join one other. Experienced in General Diagnostic, Orthopedic, US and Doppler, NM, and CT. Contact R. Dennis Davis, MD, Box 242, Sun Valley, ID 83353, or phone (208) 622-3323, ext 165.

IDAHO. Opportunity for high quality of life, low cost of living in beautiful Idaho—sunbelt of the Pacific northwest. Join Family Practice teams at one of six multi-site community/migrant health centers providing primary care to rural communities. Outstanding four-season recreation, malpractice insurance paid, generous continuing education, competitive salary and benefits, loan repayment potential, and opportunity to provide OB services. Send résumé to Dean Hungerford, Idaho Primary Care Association, PO Box 6756, Boise, ID 83707; or call (208) 345-2335.

NEUROLOGIST BC/BE. Needed to join rapidly expanding multispecialty group practice in Reno, Nevada (population 350,000). Fee-for-service and pre-paid health care. EEG, EMG, and general Neurology practice with active clinic and hospital bases. Excellent compensation and benefits package including stock options, paid malpractice, and relocation expenses. Interested individuals should submit a CV in confidence to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645, Attn: Janet R. McGee, Manager, Physician Recruitment.

BC/BE FAMILY PRACTITIONER for nonprofit community clinic in redwood country. Prefer OB/Pediatrics training, but OB negotiable. C-sections optional. Quality care for underserved and more affluent in rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

INTERNIST, University trained, wanted to join three physician group in the heart of the beautiful coastal redwoods. Active, varied, quality practice in a friendly community far from the city's woes, yet one hour by plane from San Francisco. Send CV to Timm Edell, MD, 2773 Harris St, Eureka, CA 95501.

INTERNAL MEDICINE. BC female Internist with successful established practice in the San Gabriel Valley of southern California seeks BC/BE energetic, imaginative Internist as associate. No investment. Guaranteed salary plus. Send CV/letter to SGHS, PO Box 2114, San Gabriel, CA 91778.

FACULTY POSITIONS. The San Jose Medical Center Family Practice Residency Program has an opening for full-time and part-time faculty. Positions include direct patient care (including OB), resident teaching and administrative duties. Program affiliated with Stanford University School of Medicine. Competitive salary and benefit package. Please direct inquiries to Robert Norman, MD, Director, 25 N. 14th St, Ste 1020, San Jose, CA 95112; (408) 977-4507.

LARGE MULTISPECIALTY PRIVATE GROUP PRACTICE RECRUITING FAMILY PRACTITIONER. Must be BC/BE. Excellent opportunity for qualified physician in very desirable high growth area of southern California. Congenial staff, excellent working conditions, and fringe benefits. Salary negotiable. Submit CV to George W. Kanaly, PhD, President, Riverside Medical Clinic, 3660 Arlington Ave, Riverside, CA 92506.

PHYSICIANS WANTED

SAN FRANCISCO

The San Francisco General Hospital AIDS Activities Division of the Department of Medicine of the University of California, San Francisco, is seeking applicants at the Assistant Clinical Professor level. Applicants should have completed a residency in Internal Medicine, Family Practice, and be certified by the appropriate review Board. Additionally, applicants should have received post-residency training in Family Practice, General Internal Medicine, or in a specialty relevant to AIDS such as Medical Oncology, Infectious Disease, or Clinical Epidemiology. The individuals hired will be responsible for the care of AIDS patients, teaching on all levels, and are expected to participate actively in division research activities. Outpatient care is expected to be based in the SFGH AIDS Clinic. Inpatient care will be conducted at SFGH. Applicants should have demonstrated excellence in providing AIDS patient care and in medical teaching. Please submit current CV and three letters of reference to:

Paul Volberding, MD
Search Committee Chair
AIDS Activities Division
Building 80, Ward 84
San Francisco General Hospital
995 Potrero Ave
San Francisco, CA 94110

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FAMILY PRACTITIONERS AND INTERNISTS needed part-time for staffing ambulatory care clinic. Our clinic operates seven days a week during days and evenings and provides episodic care on a same-day basis. Our patients are from a growing Sacramento community with good cost of living. Physicians may choose to work one to 10 half-days or evenings per week with wide flexibility. Full benefits and retirement if working six or more half-days a week on a steady basis. We are a successful, stable medical group experiencing robust growth. Please call John Petitt, MD, (916) 973-5560 or send CV to John Petitt, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825.

VENTURA (SOUTHERN CALIFORNIA). Multispecialty group of 42 physicians has a position available for a BC/BE Psychiatrist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Psychiatrist, 2705 Loma Vista Rd, Ventura, CA 93003.

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(Continued on Page 496)

HELPING TO ACHIEVE THE FOUR GOALS[1] OF ANTIHYPERTENSIVE THERAPY...

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

Controls blood pressure[2-6]

Maintains well-being[2-6]

Helps prevent end-organ complications[7,8]

Helps reduce cardiovascular risks[2,5,9]

90 mg SR bid

0930A9

Please see brief summary of prescribing information on next page.

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

EFFECTIVE MONOTHERAPY WITH HIGH PATIENT ACCEPTANCE

Starting Dosage:

90 mg bid*

Also Available: 120-mg capsules

*Dosage must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily.

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules
CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) or have been observed in angina trials. In many cases, the relation to drug is uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/89

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Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
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STOP LESIONS FROM SURFACING

An alarming rise in the incidence of genital herpes points to the need for better disease treatment. Fortunately, long-term maintenance therapy with ZOVIRAX® can help keep herpes patients lesion-free. In controlled studies of 4 to 6 months' duration, recurrences were totally prevented in up to 75% of patients. And during two years of clinical use, daily therapy has been shown to be generally well tolerated.[1] One capsule TID...the best way to stop lesions from surfacing.

Reference. 1. Data on file, Burroughs Wellcome Co

ZOVIRAX®
(acyclovir) **capsules**

Keeps herpes patients lesion-free longer

Please see brief summary of prescribing information on next page.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

Burroughs Wellcome Co.,
Research Triangle Park,
North Carolina 27709

ZOVIRAX®
(acyclovir) capsules

Daily therapy helps keep patients lesion-free longer*

Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories.

First Episodes (primary and nonprimary infections – commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy, the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY – Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS – Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤10 ml/min/1.73 m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"– Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).

Store at 15°-30°C (59°-86°F) and protect from light and moisture.

U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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(Continued from Page 490)

NORTH CALIFORNIA BE/BC INTERNIST wanted to join busy solo practice part- or full-time in Sierra foothills. Send CV to Number 143, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

HEMATOLOGIST/ONCOLOGIST, WASHINGTON STATE BC/BE. Immediate opportunity to take over established practice within the Hematology/Oncology (three and one-half physician) Division of the Rockwood Clinic, a 60 member multispecialty group. Competitive salary and benefits leading to early shareholder status. Spokane (metropolitan population 350,000) offers affordable housing, excellent schools, cultural activities, and unlimited outdoor recreation. Send CV to Colleen Mooney, Recruitment Coordinator, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

VENTURA (VENTURA COUNTY). Multispecialty group of 42 physicians has immediate positions available for two BC/BE Family Practitioners. Openings are available in each of our offices, located in Ventura, Camarillo, and Oxnard. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Family Practitioner, 2705 Loma Vista Rd, Ventura, CA 93003.

THIRD GASTROENTEROLOGIST for HMO in northern California wine country. Excellent salary, fringe benefits and life-style. Contact Richard Permutt, MD, 401 Bicentennial Way, Santa Rosa, CA 95403.

INTERNAL MEDICINE. San Francisco bay area—immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical housestaff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

NEUROLOGIST
for Full-Time Position in San Francisco Bay Area

Nation's largest HMO Kaiser Permanente seeks BE/BC Neurologist for immediate opening. EEG experience necessary; EMG a plus. Resident teaching opportunities. Academic affiliations encouraged. Competitive compensation and outstanding benefits including paid vacation, continuing education, life/medical/dental insurance, professional liability, retirement plans and full shareholdership within three years with profit-sharing. Send CV to:

Joel Richmon, MD
Dept of Neurology
Kaiser Permanente Medical Center
280 W. MacArthur Blvd
Oakland, CA 94611
Phone: (415) 596-6511

CAN YOU AFFORD TO MISS THIS OPPORTUNITY?

INTERNAL MEDICINE/FAMILY PRACTICE POSITION IN SOUTHERN CALIFORNIA

Enjoy a professional, challenging, growth opportunity with successful Internal Medicine private practice.

This position offers an excellent guarantee, bonus, malpractice, benefits, CME, and partnership potential.

Located in a lovely suburban community in southern California.

Send inquiries and CV to:

DAR & Associates

Physician Recruiters
250 N. Robertson Blvd, Suite 405 • Beverly Hills, CA 90211
(213) 277-7331 / (800) 922-7PHY

INTERNIST to join three man group in Alaska's southernmost city, Ketchikan. Long established medical practice. Boating, sailing, hiking, and fishing and hunting in season. Guaranteed salary and excellent benefits. Send CV to Arthur Wilson, Jr, MD, Box 8678, Ketchikan, AK 99901; (907) 225-4104.

OBSTETRICIAN/GYNECOLOGIST, NEUROLOGIST, NEUROSURGEON for progressive multispecialty group of over 21 physicians within one and a half to three hours of the San Francisco bay area, Yosemite, and Lake Tahoe. Tracy, located in the San Joaquin Valley, has a diversified economy with excellent schools. Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package including malpractice insurance. Reply with CV and references to Physician Recruitment, Eaton Medical Group, 445 W. Eaton Ave, Tracy, CA 95376.

OCCUPATIONAL/FAMILY PRACTICE. The Pacific northwest's leading outpatient medical provider has opportunities for Primary Care Physicians to join an expanding 150 person medical group. Full/part-time openings throughout California and Seattle-Tacoma, Washington. Prior outpatient/occupational experience preferred. Attractive package includes competitive base salary plus incentive program, malpractice insurance, comprehensive benefits, 401(k) plan, vacation/sick/holiday/CME. Opportunity for advancement for energetic, hard-working physician committed to quality health care. Join our dynamic team of health care professionals. Contact Robin Smith, Director, Personnel, Readi-Care/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

GENERAL SURGEON BC for full-time staff of specialty oriented referral hospital of Indian health service. Competitive salary and generous fringe benefits, reply to E. K. Mehne, MD, Gallup Indian Medical Center, Gallup, NM 87301, or (505) 722-1000. EEO employer.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented (first year guaranteed $70,000) with advancement to full partnership after one year. Excellent fringe benefits. If interested. CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

OB/GYN NORTHERN CALIFORNIA. Position available for BE/BC OB/GYN in 10 person department with new LDR suite, family centered Obstetric practice as well as full Gynecology practice. 20 miles south of San Francisco, adjacent to large wooded areas, and easy access to ocean. Prepaid medical group with competitive salary and very generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

WASHINGTON. Openings for career oriented Emergency Physicians, BE/BC in Emergency or Primary Medical specialty. In a Seattle metropolitan hospital with 48,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 S. 43rd St, Renton, WA 98055.

ORTHOPAEDIST
Southern California

Orthopaedic Surgeon (Board certified preferred) needed for lucrative, expanding medical practice in Los Angeles area specializing in Worker's Compensation. California license needed as of starting date.

Primarily office practice. Light elective surgical schedule can be limited to arthroscopies.

Virtually no call, evenings or weekends.

Excellent starting salary with possible partnership in less than one year.

Send letter and CV to:

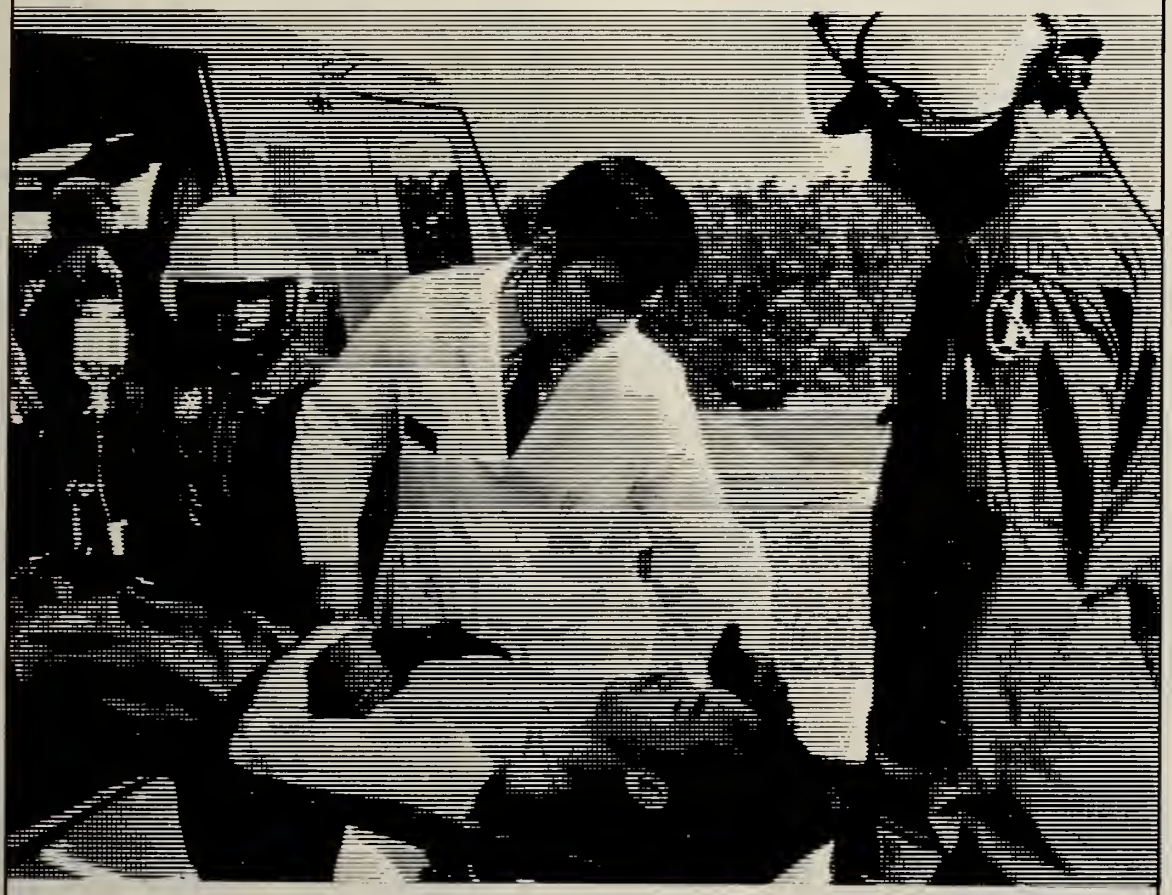
Department WJO
8306 Wilshire Blvd, #7727
Beverly Hills, CA 90211

(Continued on Page 498)

PHYSICIANS, A WEEKEND WITH THE RESERVE ISN'T JUST ANOTHER DAY AT THE OFFICE.

It's not just different in the Army Reserve, there are opportunities to explore other phases of medicine, to add knowledge, and to develop important administrative skills. There are enough different needs to fill right in your local Army Reserve unit to make a weekend a month exciting and rewarding.

Explore the possibilities. Call our officer counselor: **1-800-USA-ARMY**



ARMY RESERVE. BE ALL YOU CAN BE.

(Continued from Page 496)

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

FAMILY PRACTICE/SACRAMENTO. Due to continued growth, positions for Family Practice are now available at Kaiser Permanente Medical Center, south Sacramento. Our salary is very competitive and we have an outstanding retirement and benefits package. Your practice at Kaiser will allow insulation from the headaches and financial uncertainty of private office practice, while fostering your professional growth at a first rate medical center. For further information, please contact Jack Berger, MD, Assistant Chief, Department of Medicine, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823; or call (916) 686-2267.

WASHINGTON, CASCADE MOUNTAINS. Three physician Family Practice seeking fourth Family Practitioner. Challenging rural practice in recreational area 80 miles east of Seattle. Interest in Emergency Medicine necessary, OB optional. Ski areas, lakes, wilderness, and pleasant family oriented community. Contact Paul Schmitt, MD, 201 Alpha Way, Cle Elum, WA 98922; (509) 674-5331.

FAMILY PRACTITIONER. Multispecialty group located in San Luis Obispo, California on the central coast, seeking a BE/BC physician. Fringe benefits plus practice costs paid and immediate shareholder status. Submit your CV to Administration-Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

GENERAL INTERNIST, with or without subspecialty training, being sought to join busy seven member Internal Medicine practice in downtown Sacramento. One to two years of guaranteed salary to start. Contact Joshua Hoffman, MD, at (916) 733-5097, or send CV to 2801 K St, #520, Sacramento, CA 95816.

BC PHYSICIANS MANAGED CARE

Cost Care, the nation's leading health care cost management company, is seeking full- or part-time BC physicians to staff the Medical and Mental Health Services departments. Ideal candidates will have:

- Three to five years clinical experience in a managed care setting
- Utilization Review expertise
- Strong interpersonal skills

Send résumé/CV to:

Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

PHYSICIANS WANTED

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

Allergy	Ophthalmology
Anesthesiology	Orthopaedics
Cardiology	Otolaryngology
Dermatology	Pediatrics
Family Practice	Psychiatry
General and Vascular Surgery	Urgent Care
OB/GYN	Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

NORTHERN CALIFORNIA. The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. University associated residency program. Competitive salary and comprehensive benefits package. 90 miles from San Francisco and Sierra skiing. California license required. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678.

NORTHWEST. Family Practice, Internal Medicine, OB/GYN private practices available now outside Portland, Seattle, and scenic communities in California, Idaho, Colorado, and Montana. Group or hospital sponsored. Specific details available. CV to Jean Erickson, Prosearch, 305 NE 102nd Ave, Portland, OR 97220-4199; (503) 256-4488.

MEDICAL ADMINISTRATOR (BILINGUAL) to supervise and coordinate activities of workers in the medical office. Will not be required to examine or treat patients, only provides information in the absence of the examining physician. Must have medical administrator or medical doctor. Salary $4,500 per month. Job site Los Angeles, California. Send this ad and résumé to Job # DH 0521, PO Box 9560, Sacramento, CA 95823-0560 not later than May 9, 1989.

SAN FRANCISCO BAY AREA. Family Physician or Internist wanted to join newly formed women physician group. Competitive salary with malpractice coverage, vacations and sick leave, and disability insurance. Send CV to Number 152, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN—IMMEDIATE OPPORTUNITIES for BC/BE physicians in northern California. Excellent salary compensations with benefits. Also private practice available in San Francisco area suburb. Please send CV or call Mary Frances Malone, Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

GENERAL INTERNIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Norman Olson, Chief of Medicine, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Norman Olson, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

DIAGNOSTIC RADIOLOGIST. BC/BE Radiologist wanted to join two BC Radiologists in north Sacramento Valley. The practice is affiliated with two rural hospitals and a large multispecialty clinic. The practice includes ultrasound mammography, limited CT, and nuclear imaging. No MRI or interventional procedures. Competitive salary leading to partnership. Forward CV with references to Number 150, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE AND INTERNAL MEDICINE opportunities available now—Montana Rockies new primary care clinic. Offers competitive income and the best outdoor recreation anywhere. Call (503) 256-4488, Prosearch, 305 NE 102, Portland, OR 97220.

INTERNIST BC/BE to join 35 year practice. Sherman Oaks. Good family area, early association, plus planned, limited night, weekend call. CV to Number 149, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WANTED BC/BE PEDIATRICIANS

Nighttime pediatrics clinic. For information see article in *Contemporary Peds,* July 1987. Part-/full-time 20 to 40 hours per week. Salary negotiable. Inquire c/o

Jed Dunford
279 East 5900 South
Murray, UT 84107

(Continued on Page 500)

Team Support...Every Day And When You Need Us Most

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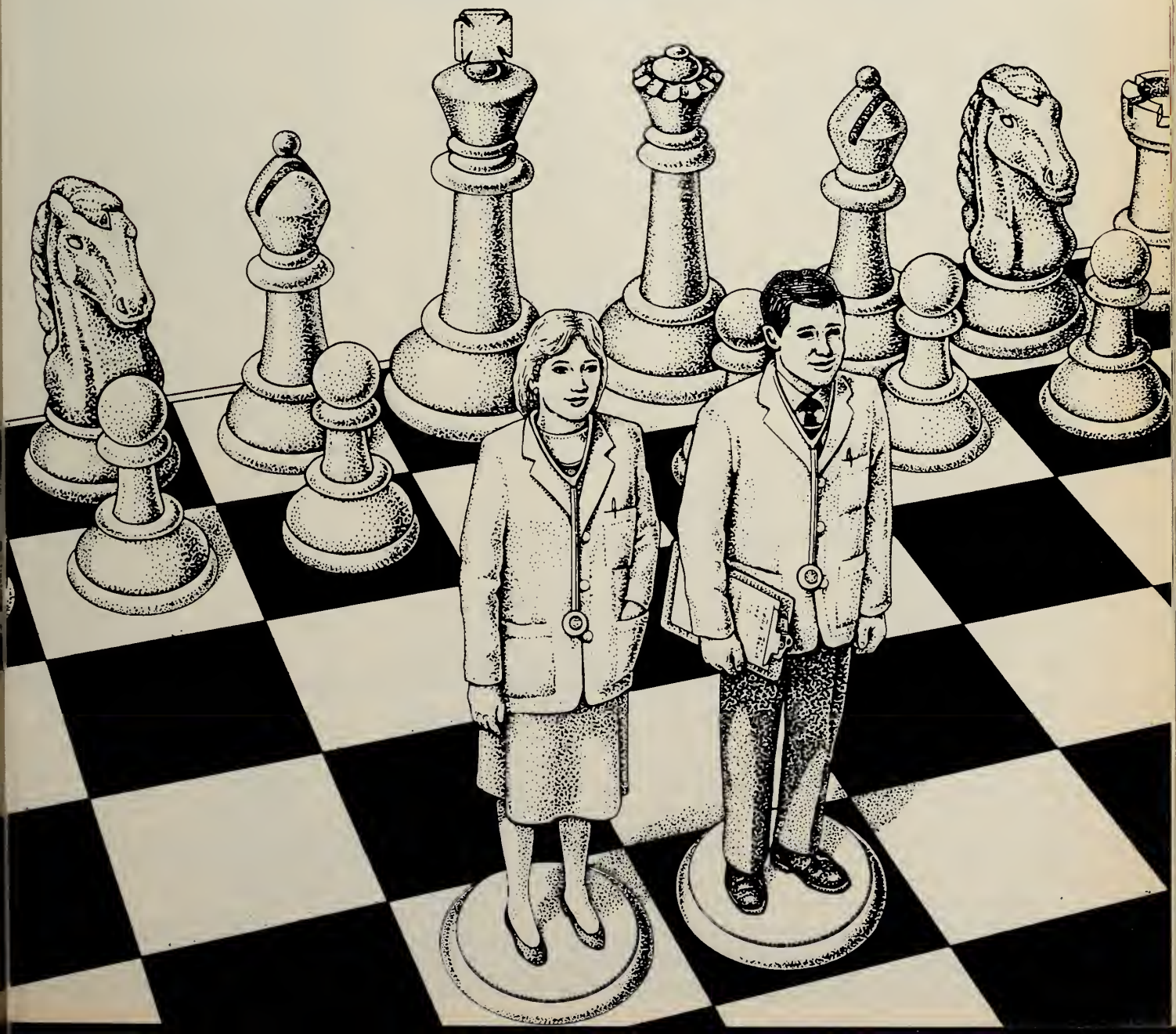

(Continued from Page 498)

PHYSICIANS WANTED

FAMILY PHYSICIAN—SAN DIEGO

Well-established (40 years) three Family Practitioner group seeks Family Practitioner to replace retiring associate. Attractive salary plus incentives. Possibility of partnership after two years. Well-rounded Family Practice—Pediatrics to Geriatrics. Send CV to **Gordon Lillie, MD, 7043 University Ave, La Mesa, CA 92041.**

STUDENT HEALTH PHYSICIAN. Excellent opportunity for BC Primary Care Physician to join 3 plus MD clinic providing quality ambulatory care at a desirable northern California university location. Full-time 11 month position. Part-time considered. Apply promptly with CV/cover letter to Sonoma State University, Student Health Center, Rohnert Park, CA 94928; (707) 664-2926 (voice), (707) 664-2751 (TDD). AA/EOE.

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Parkway, San Jose, CA 95119; (408) 972-6428.

FAMILY PRACTICE, PUGET SOUND. 27 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to John Houser, Executive Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

IMMEDIATE OPENINGS for part-time or full-time Surgical House Officer positions. Must have California license and at least one year of general surgery training. Competitive hourly wage and malpractice insurance provided. Call Dr E. Tsoi at (415) 668-1000.

PULMONOLOGIST, BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Norman Olson, MD, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

MONTEREY PENINSULA, CALIFORNIA. General Surgeon to join another surgeon in a multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established group practice. Excellent office, lab, x-ray department. Outstanding community hospital. Submit CV, availability date to Gerard Martin, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

CIGNA

MEDICAL DIRECTOR

CIGNA Healthplan of northern California needs a Medical Director who has two plus years of utilization management or quality assurance experience and is BC in California. The successful candidate will be responsible for monitoring the quality and efficiency of our medical system, assisting with provider recruitment, and providing day to day management of all aspects of the medical operations portion of the Healthplan. For prompt consideration, please forward your résumé in confidence to:

Vice President and General Manager
CIGNA Healthplan of
Northern California
1999 Harrison St, Ste 1000
Oakland, CA 94612

PHYSICIANS WANTED

SAN DIEGO STATE UNIVERSITY
STUDENT HEALTH SERVICES PHYSICIAN II

Ten month position. BC required. Family Practice strongly preferred. Salary range $5,488 to $6,642. EOE/AA/Title IX Employer. Interested candidates submit CV and letter to **Kevin Patrick, MD, Director, Student Health Services, San Diego State University, San Diego, CA 92182.**

FACULTY POSITION available July 1, 1989, in community-based University of Washington Family Practice residency in beautiful Pacific northwest. Responsibilities to include patient care, resident teaching and supervision, and limited program administration. Obstetrics required. Salary and benefits based on experience. Direct CV and inquiries to Philip D. Cleveland, MD, Director, Family Medicine Spokane, S. 510 Cowley, Spokane, WA 99202; (509) 624-2313.

FAMILY PRACTICE, CASHMERE, WASHINGTON for two MD office with call sharing by four MDs. Scenic location in fruit growing valley at east edge of Cascades and 10 miles west of Wenatchee. Highly rated schools, and recreation is tops. Edgar A. Meyer, MD, 303 Cottage Ave, Cashmere, WA 98815; (509) 782-1541.

WASHINGTON. General Internist BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is composed of 32 physician multispecialty group. Guaranteed income, plus excellent benefits. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

WASHINGTON. BC/BE Family Physician for a clinic-based immediate care center. The clinic is a 32 physician multispecialty group. Guaranteed income with excellent benefit package. Ideal opportunity for active practitioner who wants to slow down. Send CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

INTERNAL MEDICINE. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an Internist for full-time work. Competitive salary. Excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

FAMILY PRACTITIONER. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks a Family Practitioner for full-time work. Competitive salary. Excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

OREGON. General Internist (BC/BE) sought for busy practice. 10 member multispecialty group. Beautiful rural community. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

FAMILY PRACTICE. Fantastic opportunity for the right physician! We operate six community health centers in central California. Currently we have two openings. One is for a fourth provider at our Wofford Heights Clinic located in a beautiful mountain lakeside resort. The second opening is in Frazier Park, a mountain resort area located one hour north of Los Angeles. Malpractice paid in full. This is a rare opportunity to combine a very attractive life-style with an excellent salary and benefit package. Call George Johnston, (805) 845-3731 for details or write Clinica Sierra Vista, PO Box 457, Lamont, CA 93241.

MEDICAL DIRECTOR. Community health clinic is seeking a Family Practice Physician to be responsible for the overall functioning of our medical program at our six clinics. Position is at our main clinic near Bakersfield in central California. Should be licensed to practice medicine in California and have proven clinical and administrative skills. Contact Stephen W. Schilling, Executive Director, Clinica Sierra Vista, PO Box 457, Lamont, CA 93241; (805) 845-3731.

PHYSICIANS WANTED

INTERNISTS

Practice in beautiful

Northern California

Hospital-based internists immediately needed at prestigious 132-bed Redding Medical Center. Large open-heart surgery program. Practice limited to inpatient general med. Xlent benefits (CME, vacation), min. guarantee of $125,000 annual take-home pay, plus FFS incentives, paid malpractice, and hospital provides billing. Flexible rotating call schedule. Incredible opportunity!

Hospital lies in the shadow of Mt. Shasta. Great recreational and family area. Contact:

Gary L. Groves, MD
(714) 825-4401 in CA
or (800) 338-4798

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128.

SAN FRANCISCO BAY AREA. Large multispecialty, multi-facility group practice is seeking a BC/BE physician to join their expanding Occupational Medicine Department. Range of practice includes pre-employment physicals, diagnostic evaluations; treatment of on-the-job injuries. Competitive salary, excellent benefits and incentive plan, paid malpractice. Located in the South Bay which offers many cultural facilities, recreational activities, fine dining, outstanding scenery and climate, and easy access to San Francisco, Monterey, and the Sierra Nevada. For further information, please send CV or contact Maureen Forrester, Physician Recruitment, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

INTERNIST. Live and work in the beautiful Sierra foothills. Four busy Internists are looking for fifth. Easy access to San Francisco bay area, Tahoe, great outdoors. Contact Bob Hartmann, MD, 815 Court St, #7, Jackson, CA 95642; (209) 223-3837.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

(Continued on Page 502)

AIM HIGH

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Most administrative responsibilities are in the hands of others, giving you the time to give full attention to the patients' needs. Our hospitals are staffed with dedicated, competent professionals to assist you.

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Find out more about Air Force medicine. Contact your nearest Air Force recruiter. Call

1-800-423-USAF
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AIR FORCE

(Continued from Page 500)

PHYSICIANS WANTED

FAMILY PRACTICE/URGENT CARE—IMMEDIATE OPPORTUNITIES
for BC/BE physicians in northern and central California. Excellent salary compensations and benefits. Also private practices available in Sacramento, Modesto-Stockton area, and Contra Costa County. Please send CV or call **Mary Frances Malone, Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.**

WOMEN'S PRIMARY CARE GROUP FORMING. A group of women Primary Care Physicians is considering forming a new medical group in the South of Market area of San Francisco. This effort is being formed by women who want flexible schedules, to share a practice, and to work part time. St Luke's Hospital is helping to form this group. If interested, please call (415) 641-6543 or write Victoria Sweet, MD, c/o Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110.

LOS ANGELES COUNTY—FAMILY PHYSICIAN. There are now two attractive opportunities for Family Physicians in the Los Angeles area. Join a busy, five member group or select a salaried position in a small urgent care center. For more information, send your CV to Manager, Professional Relations, Humana Inc, Dept HH-4, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

BC/BE FAMILY PRACTICE PHYSICIAN wanted to join five physician multispecialty group (three Family Practitioners, one General Surgeon, and one Internist) in northern California. Two and a half hours from San Francisco, two hours from Lake Tahoe, one hour from Sacramento. Contact C. J. Shieh, MD, 225 Spruce St, Gridley, CA 95948; (916) 846-5655.

Department of Health Services
State of California

MEDICAL CONSULTANT I EXAMINATION ANNOUNCEMENT

Salary Range $5,182 to $6,771 Monthly

Positions with the Department of Health Services exist statewide. Some of the responsibilities of the Medical Consultant I include: Specific case reviews to determine medical necessity and appropriateness of service, by health care providers, for Medi-Cal covered services. Provides input into development of policies on the administration of medical aspects affecting the Department's programs. Interfaces with provider groups, hospitals, quality assurance/utilization review committees, and medical societies to encourage the delivery of quality care to Medi-Cal patients.

MINIMUM QUALIFICATIONS

- Possession of the legal requirements for the practice of medicine in California as determined by the California Board of Medical Quality Assurance or the Board of Osteopathic Examiners, and
- One year of experience in the practice of medicine beyond the first year of residency training.

DESIRABLE QUALIFICATIONS

1. BC or BE.
2. Past or present participation in peer/utilization review.
3. Broad and recent experience in practice of medicine.

This examination will consist of a comprehensive qualifications appraisal interview.

HOW TO APPLY

State application forms (678) may be obtained from the State Personnel Board, the State Employment Development Department, or the Department of Health Services' office listed below.

The tentative final filing date for this exam is May 26, 1989. Completed applications and CVs and/or any questions should also be directed to this office:

Department of Health Services
Field Services Branch
714 P St, Room 1516, Sacramento, CA 95814
(916) 445-9166

"An equal opportunity employer
Women, minorities, and disabled are encouraged to apply"

PHYSICIANS WANTED

DERMATOLOGY—TWO IMMEDIATE OPPORTUNITIES
for BC/BE physician in northern California. (1) Client is offering an excellent salary compensation and benefits. (2) Opportunity to own a private practice—desirable community close to San Francisco area. Please send CV or call **Mary Frances Malone, Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.**

SOUTHWEST UNITED STATES. Private practice opportunity to join seven very busy Orthopedic Surgeons. Completion of a spinal fellowship is mandatory. A highly competitive guaranteed income and benefit package will be provided. Contact Bob Suleski, 250 Regency Ct, Waukesha, WI 53186; 1 (800) 338-7107.

MONTEREY PENINSULA, CALIFORNIA. BC/BE General Internist to join four other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established clinic practice. Excellent office, lab, x-ray department. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

PRACTICES AVAILABLE

SAN DIEGO—INTERNAL—FAMILY—OB/GYN—PEDIATRIC AND OTHER SPECIALTY PRACTICES AVAILABLE. Long established—doctors retiring. Various prices—low down payments. Call CBI, the San Diego professional practice sales specialists, (619) 283-7009.

NORTHERN ARIZONA FAMILY PRACTICE FOR SALE. Well-established, solo practice. Share in call group. Purchase office building optional. Ideal location for family—good schools, university, plenty of outdoor activities. Kirk R. Stetson, MD, Flagstaff, Arizona; (602) 774-6671.

OPHTHALMOLOGY, SOUTHERN CALIFORNIA. 55 year old busy group practice for sale by last remaining solo Ophthalmologist, who is semi-retiring. Beautiful, clean coastal city is great place to raise family. Send CV with cover letter to Number 147, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE OR FAMILY PRACTICE. Established Internal Medicine practice (30 years). Opportunity to grow or slow down. Santa Cruz, California. Nicely decorated, spacious office, two blocks to hospital, lab and x-ray equipment. Reasonable terms. Retiring, will stay on to introduce. Available July 1989. Call or write Wm. R. Blade, MD, 1510 Seabright Ave, Santa Cruz, CA 95062; (408) 423-0963.

BEAUTIFUL NAPA VALLEY, CALIFORNIA. Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

NAPA VALLEY—INTERNAL MEDICINE. Located one hour north of San Francisco. Established 30 years by physician who now wishes to retire. Excellent reputation and adjacent to hospital. 1,500 active patients. Staff can transfer and seller available for transition. Request detailed prospectus. Professional Practice Sales, (415) 665-8500.

SURGICAL PRACTICE FOR SALE. Torrance area. 35 years in same location (next door to Torrance Memorial Hospital). Terms negotiable. Call (213) 534-4744, or write to Number 151, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PRACTICE AVAILABLE. General Surgery, southern California, ideal Orange County location, established 25 years. Adjacent 175 bed full service hospital, near university, Disneyland. Fully equipped office. Senior Surgeon retiring. BC or BE required. Send résumé to PO Box 2936, Anaheim, CA 92814; (714) 778-5908.

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SPECIAL ISSUES

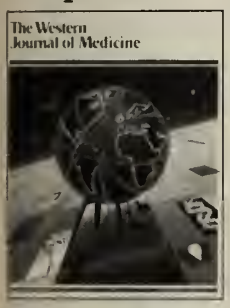
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

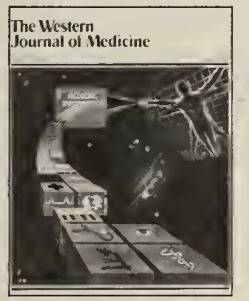
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics

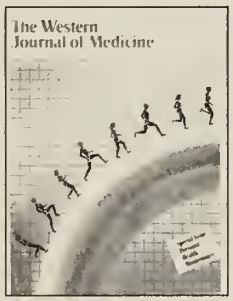


Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine

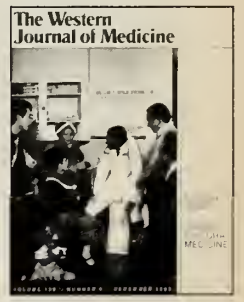
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 1-3, 1989, Pointe at South Mountain, Phoenix.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 14-17, 1989, Westin Hotel, Vail.

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Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-29, 1989, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 1-4, 1989, Ely.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-13, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and place to be announced.

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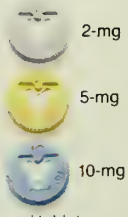

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CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

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Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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A·H·ROBINS

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: General. Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n =	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	8%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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From the Department of Psychiatry, Oregon Health Sciences University School of Medicine, Portland. Dr Kofoed is currently affiliated with the Department of Psychiatry, Dartmouth Medical School, Hanover, New Hampshire.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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Brief Summary

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Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General* — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests — False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions — No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported, it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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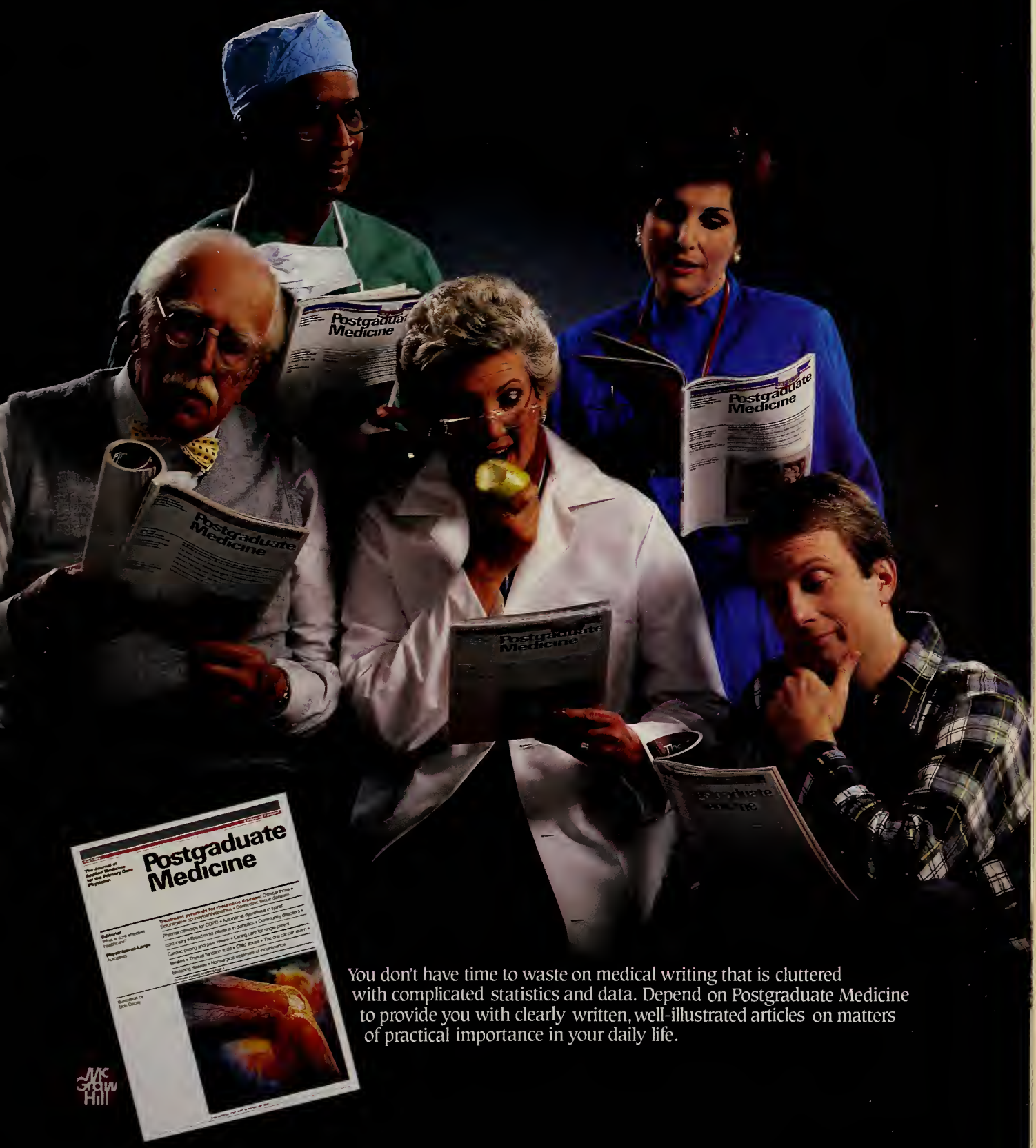

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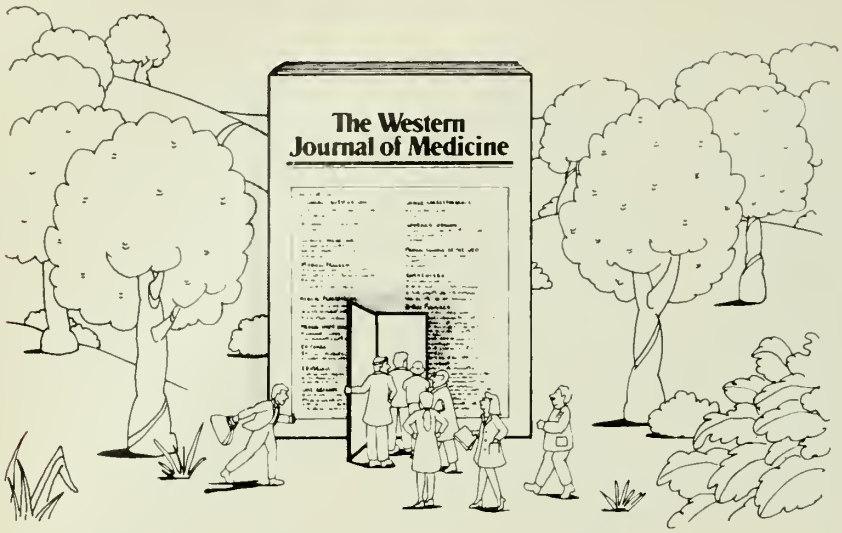

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BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE
There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:
1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987; 9(4):395-399.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 1—**1989 Arizona Medical Association Annual Meeting—Current Perspectives.** The Pointe at South Mountain. Thurs. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

July 21-22—**American In-Vitro Allergy/Immunology Society Annual Program.** American In-Vitro Allergy/Immunology Society at San Diego Marriott Hotel and Marina. Fri-Sat. 12 hrs. $200. Contact: Betty Kahler, PO Box 459, Lake Jackson, TX 77566. (409) 297-5636.

September 21-22—**Modern Approaches to Allergy and Clinical Immunology.** UCSF at Hyatt Union Square, San Francisco. Thurs-Fri. 15 hrs. $300. Contact: UCSF.

ANESTHESIOLOGY

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 23-24—**Advanced Cardiac Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

June 24—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 525)

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SPECIAL ISSUES

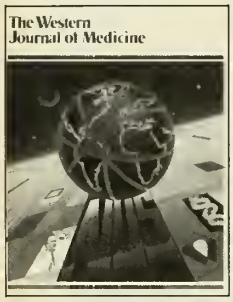
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

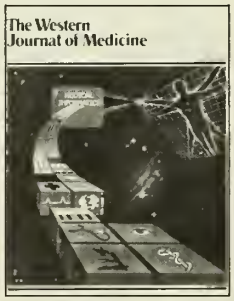
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



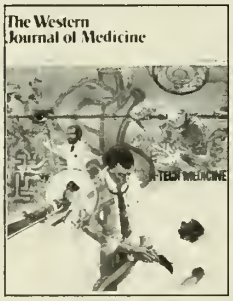
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



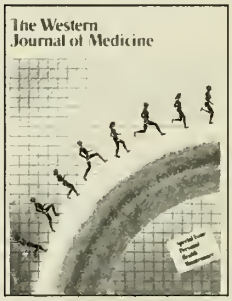
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



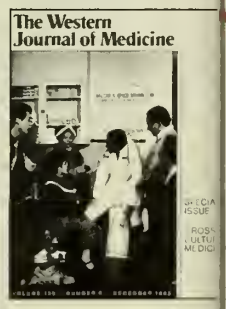
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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HELPING TO ACHIEVE THE FOUR GOALS[1] OF ANTIHYPERTENSIVE THERAPY...

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

Controls blood pressure[2-6]

Maintains well-being[2-6]

Helps prevent end-organ complications[7,8]

Helps reduce cardiovascular risks[2,5,9]

90 mg SR bid

0930A9

Please see brief summary of prescribing information on next page.

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

EFFECTIVE MONOTHERAPY WITH HIGH PATIENT ACCEPTANCE

Starting Dosage:

90 mg bid*

Also Available: 120-mg capsules

*Dosage must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily.

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules
CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system, these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) or have been observed in angina trials. In many cases, the relation to drug is uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope
Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.
Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst
Dermatological: Petechiae, pruritus, photosensitivity, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, noctuna, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/89

References: 1. Staessen J, Fagard R, Lignen P, et al: *Pract Cardiol* 1986;12(5):55-65. **2.** Massie B, MacCarthy EP, Ramanathan KB, et al: *Ann Intern Med* 1987;107(2):150-157. **3.** Weir MR, Josselson J, Giard MJ, et al: *Am J Cardiol* 1987;60:36I-41I. **4.** Frishman WH, Zawada ET Jr, Smith LK, et al: *Am J Cardiol* 1987;59:615-623. **5.** Pool PE, Seagren SC, Salel AF: *Am J Cardiol* 1985;56:86H-91H. **6.** Pool PE, Seagren SC, Salel AF: *Cardiol Board Rev* 1986;3(10):77-91. **7.** Sunderrajan S, Reams G, Bauer JH: *Hypertension* 1986;8:238-242. **8.** Amodeo C, Kobrin I, Ventura HO, et al: *Circulation* 1986;73(1):108-113. **9.** Schulte K-L, Meyer-Sabellek WA, Haertenberger A, et al: *Hypertension* 1986;8:859-865.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 520)

July 15—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: Deborah Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

June 2-3—**Southwestern Regional Cutaneous Flap Workshop.** UCLA Center for Health Sciences. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

June 25—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 16—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

June 23-24—**Advanced Cardiac Life Support.** Center for Health Education at Long Beach. Fri-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 24-25—**11th Annual Poison Center Symposium: Emergency Medicine and Toxicology.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $280. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

May-June—**Seminars in Cytopathology 1989.** UCSF at Health Sciences Room 300. Thurs/monthly. 12 hrs. $140 full series/$30 single. Contact: UCSF.

May 21—**The California Tumor Tissue Registry's Semi-Annual Slide Seminar on Skin and Skin Appendage Tumors.** Sat. Contact: CTTR, 1200 N State St, Box 40, Los Angeles 90033. (213) 226-4614.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 14-16—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt Union Square. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 30-July 2—**California Society of Internal Medicine: 44th Annual Meeting.** California Society of Internal Medicine at Maui Marriott Hotel, Kaanapali Beach. Fri-Sun. 4 hrs. $125. Contact: Cynthia Eaton, PO Box 880606, San Francisco 94188-0606. (415) 882-5198.

September 4-5—**International Conference on Thyroid Metabolism.** UCI at Queen Mary Hotel, Long Beach. Mon-Tues. Contact: UCI.

(Continued on Page 526)

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(Continued from Page 525)

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

OB/GYN

June 2-3—**Perinatology: Fact and Friction.** Fri-Sat. 11 hrs. Contact: Marianne Gray, (213) 380-1790.

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

June 30-July 4—**7th Annual Controversies in OB/GYN.** UCI at Mauna Kea, Hawaii. Fri-Tues. Contact: UCI.

July 29-August 8—**Update in Urogynecology.** UCI at Hawaii. 1 week/2 days. Contact: UCI.

October 12-13—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott Hotel, Newport Beach. Thurs-Fri. Contact: UCI.

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

OPHTHALMOLOGY

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

September 15-16—**Uveitis Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Quail Lodge, Carmel Valley. Fri-Sat. Contact: UCSF.

PEDIATRICS

June 10—**Atherosclerosis; Pathogenesis and Screening.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Hypertension in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

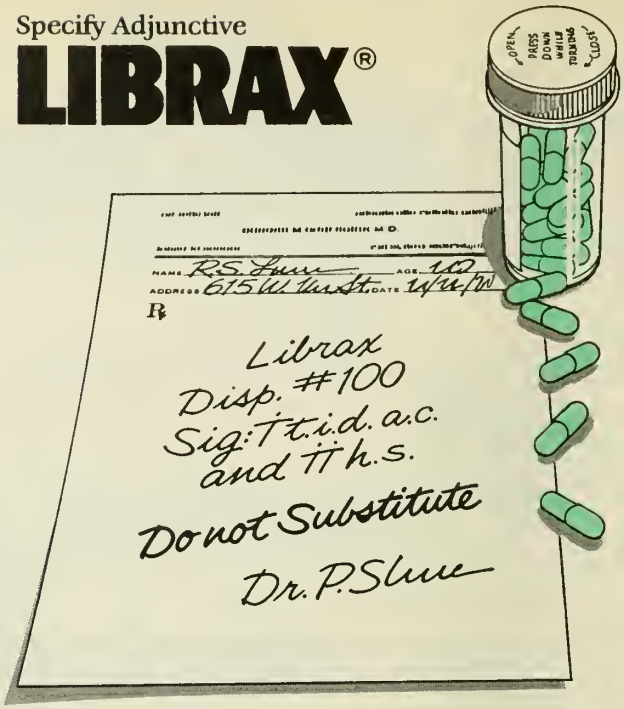
June 10—**Office Evaluation of Sports Injuries.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 10—**Fitness Training in Children.** Los Angeles Pediatric Society at Kaiser Permanente, Panorama City. Sat. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

(Continued on Page 531)

Specify Adjunctive

LIBRAX®



Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e g*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

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Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

In IBS,* when it's brain versus bowel,

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In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

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Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

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Please see summary of prescribing information on adjacent page.

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This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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Tablets
Vaseretic

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Once-A-Day

Vaseretic®

(Enalapril Maleate-Hydrochlorothiazide|MSD)

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: ***Hypotension:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS)

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema.* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy.* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release:* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents:* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium:* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium:* See WARNINGS, *Hydrochlorothiazide*; and PRECAUTIONS, *Drug Interactions, Hydrochlorothiazide.*

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk, however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Cardiovascular:* Syncope, orthostatic hypotension, palpitations, chest pain, tachycardia. *Gastrointestinal System:* Abdominal pain, vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous System:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, pruritus, decreased libido, rash, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN:* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*). *Gastrointestinal System:* Ileus, pancreatitis, hepatitis or cholestatic jaundice. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, rhinorrhea. *Other:* Photosensitivity, alopecia, flushing, taste alteration, glossitis. A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide—Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 341B—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

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For more information, consult your MSD Representative or see Prescribing Information.
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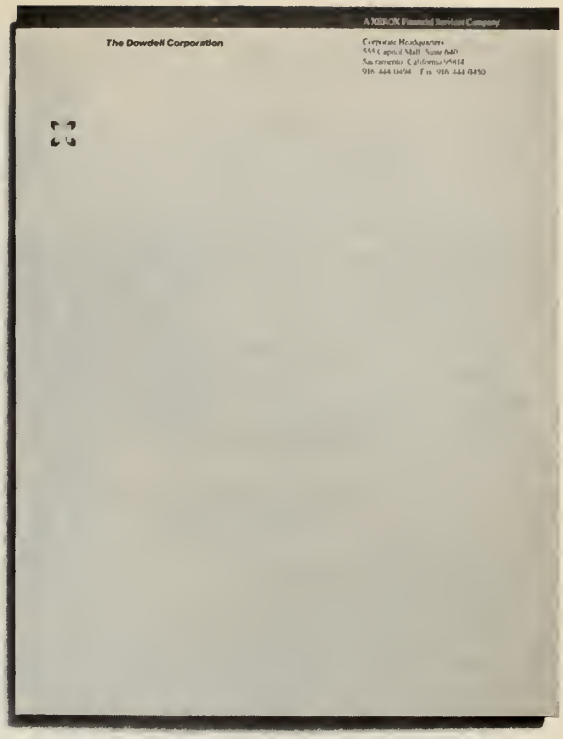

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CONTINUING MEDICAL EDUCATION

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June 16-17—**Current Concepts in Pediatric Respiratory Disease.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Fri-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

July 21-22—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

June 23-24—**Breastfeeding for Health Professionals.** UCSF at Hyatt Oakland International Airport. Fri-Sat. 10 hrs. $75. Contact: UCSF.

July 10-12—**Seminar for Physicians: Breastfeeding: A Natural World Resource.** La Leche League International at Anaheim Hilton and Towers. Mon-Wed. 16 hrs. Contact: LLLI, 9616 Minneapolis Ave, Franklin Park, IL 60131. (312) 455-7730.

July 18—**22nd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel Nob Hill, San Francisco. Thurs-Sat. 16 hrs. $275. Contact: UCSF.

August 11-13—**2nd Annual Postgraduate Course.** UCI at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

October 13-14—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

PSYCHIATRY

October 13-15—**California Psychiatric Association Annual Meeting** at Del Coronado Hotel, San Diego. Fri-Sun. Contact: Barbara Gard, 221 Main St, Ste 352, San Francisco 94105-9832. (415) 882-5196.

RADIOLOGY

July 27-30—**3rd Annual Symposium on Magnetic Resonance Imaging.** Ritz-Carleton Resort Hotel, Laguna Niguel. Thurs-Sun. 23 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 30-August 3—**Napa Valley Imaging Update: MRI 1989.** UCD at Silverado Country Club, Napa Valley. Sun-Thurs. 17 hrs. $435. Contact: Nina Musselman, (916) 453-5390.

July 31-August 4—**Modern Radiology Practice.** UCSD at Four Seasons Biltmore Hotel, Santa Barbara. Mon-Fri. 24 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 24-27—**Physics and Biology of Radiology.** UCSD at Town & Country Hotel, San Diego. Thurs-Sun. 25 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 7-10—**5th Annual Sonography Update for Physicians and Sonographers.** UCSD at San Diego Marriott Hotel and Marina. Thurs-Sun. 18 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 12-14—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center Cincinnati at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sat. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

(Continued on Page 532)

CONTINUING MEDICAL EDUCATION

(Continued from Page 531)

SURGERY

May-October—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

May 20—**6th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic Surgery Medical Group at La Jolla Marriott Hotel. Mon. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

August 5-12—**Fine Needle Biopsy Course.** UCSF at Westin Hotel, Kauai, Hawaii. 1 week. 25 hrs. $895. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

OF INTEREST TO ALL PHYSICIANS

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

May 23-26—**A Comprehensive Review for the Primary Care Provider: 16th Annual Family Practice Refresher Course.** UCD at Embassy Suites, Napa. Tues-Fri. 21 hrs. $365. Contact: UCD.

May 25-26—**5th Annual Current Issues in Anatomic Pathology.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

May 30-June 3—**Family Practice Refresher Course and Board Examination Review.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $395. Contact: UCLA.

June 1-2—**8th Annual Occupational and Environmental Medicine Symposium with Postgraduate Mini-Courses.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thurs-Fri. 17 hrs. $130. Contact: UCD.

June 4-9—**The Power of the Art: Humanism, Healing and Health Care.** Kauai Foundation for Continuing Education and The Hawaii Medical Association at Poipu Beach, Kauai. Sun-Fri. 25 hrs. $395. Contact: David J. Elpern, MD, 3420-B. Kuhio Highway, Lihue, HI 97666. (808) 245-5653.

June 11-16—**Family Practice Refresher Course.** UCI at Newport Beach Sheraton. Sun-Fri. 30 hrs. Contact: UCI.

June 19-23—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics, OB/GYN, ENT, Dermatology, Legal Aspects, Psychiatry, Ophthalmology, Toxicology, Oral Surgery, Pharmacology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 23—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 28—**AIDS Update: Essential Issues in Primary Care Management.** Alta Bates-Herrick Hospital at Alta Bates Auditorium, Berkeley. Wed. 7 hrs. $75. Contact: Mary Grim, (415) 540-1420.

June 30-July 1—**Euthanasia: An Old/New Dilemma for Physicians.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

July 9-12—**3rd Annual Family Practice Board Review.** UCSD at Hanalei Hotel, San Diego. Sun-Wed. 20 hrs. $355. Contact: Janice R. Turner, PO Box 2528, La Jolla 92038. (619) 459-9597.

July 10-13—**Family Practice Board Review Course.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Thurs. 25 hrs. Contact: Division of Family and Community Medicine, 400 Parnassus Ave, A-C9, San Francisco 94143-0900. (415) 476-1482.

July 14—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 31-August 3—**Practical Orthopaedic Sports Medicine.** Children's Hospital Oakland at Hyatt Regency, Waikoloa, Kona Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Stuart Zeman, MD, 2999 Regent St, No 203, Berkeley 94705. (415) 540-8686.

August 2-6—**Wilderness Medicine: '89.** American College of Emergency Physicians California Chapter at Squaw Valley, Lake Tahoe. Wed.-Sun. 23 hrs. $395. Contact: Eugene Allred, MD, PO Box 321, Yreka 96097. (916) 842-4667.

August 11-12—**Office Practice Enhancement: Non-invasive Diagnostic Testing.** Medical Education Collaborative at Lake Tahoe, Nevada. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 8-9—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Napa. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 13-15—**Primary Care Medicine: Principles and Practice.** UCSF at The Portman, San Francisco. Wed-Fri. 20 hrs. $385. Contact: UCSF.

October 14—**29th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott Hotel. Sat. Contact: Sylvie Tarro, (213) 641-8152.

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

IDAHO

July 27-29—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701.

August 7-8—**Northwest Regional Perinatal Conference—Current Issues in OB/GYN, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Mon-Tues. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 2-3—**University of New Mexico Department of Orthopaedics Alumni Meeting.** Nursing/Pharmacy Auditorium, University of New Mexico, Albuquerque. Contact: UNM Department of Orthopaedics, (505) 277-4701.

June 15-16—**9th Annual University of New Mexico/American College of Emergency Physicians Emergency Medicine Symposium.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

(Continued on Page 540)

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Reference. 1 Data on file, Burroughs Wellcome Co

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Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤ 10 ml/min/1.73 m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).
Store at 15°-30°C (59°-86°F) and protect from light and moisture.

U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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1. Data on file, Lilly Research Laboratories.

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AXID®

nizatidine capsules

Brief Summary

Consult the package literature for complete information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General* — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests — False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions — No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

PV 2096 AMP [013089]

Additional information available to the profession on request.

Shown left to right are William Morgan, M.D.; William Singer, M.D.; Rebecca Katz, M.D.; Mitchell Frank, M.D.; Frances de Picciotto, M.D.; Matt Young, M.D.

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Reasons To Choose Clinoril® First

TABLETS, 150 mg and 200 mg

(Sulindac|MSD)

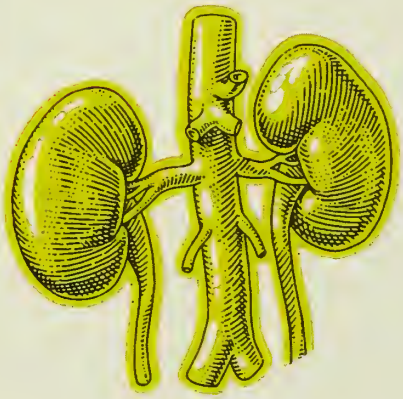
NOW AVAILABLE ON MEDI-CAL

MEDI-CAL Reimbursement Code Numbers
CLINORIL, 150-mg tablet—2047A
CLINORIL, 200-mg tablet—2048B

Prompt relief of the signs and symptoms of osteoarthritis. CLINORIL at 200 to 400 mg daily was comparable in effectiveness to aspirin 2400 to 4800 mg daily.

CLINORIL is contraindicated in patients who are hypersensitive to this product or in whom acute asthmatic attacks, urticaria, or rhinitis is precipitated by aspirin or other NSAIDs.

Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.



CLINORIL may affect renal function to a lesser extent than other NSAIDs;* however, renal adverse effects have been reported.

Caution should be exercised when administering CLINORIL to patients with conditions associated with increased risk of the effects of NSAIDs on renal function, such as those with complications associated with advanced age.

*These observations need further clarification, and, in the interim, CLINORIL should be used with caution in patients whose renal function may be impaired or prostaglandin dependent or who have a history of renal lithiasis. Such patients should be closely monitored.

No reported blunting of certain antihypertensive agents.

Edema has been observed in some patients taking CLINORIL. Therefore, as with other NSAIDs, CLINORIL should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

For a Brief Summary of Prescribing Information, please see the following page.

MSD
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For many osteoarthritic patients age 65 and older

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TABLETS 150 mg and 200 mg

(Sulindac | MSD)

Contraindications: Hypersensitivity to this product; patients in whom acute asthmatic attacks, urticaria, or rhinitis is precipitated by aspirin or other nonsteroidal anti-inflammatory agents.

Warnings: ***Gastrointestinal Effects:*** Peptic ulceration and gastrointestinal bleeding have been reported. Fatalities have occurred. Gastrointestinal bleeding is associated with higher morbidity and mortality in patients acutely ill with other conditions, the elderly, and patients with hemorrhagic disorders. In patients with active gastrointestinal bleeding or an active peptic ulcer, an appropriate ulcer regimen should be instituted, benefits of therapy must be weighed against possible hazards, and the patient's progress carefully monitored; in patients with a history of either upper or lower gastrointestinal tract disease, CLINORIL® (Sulindac, MSD) should be given under close supervision and only after consulting the ADVERSE REACTIONS section.

Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Hypersensitivity: Rarely, fever and other evidence of hypersensitivity (see ADVERSE REACTIONS), including abnormalities in one or more liver function tests and severe skin reactions, have occurred; fatalities have occurred in these patients. Hepatitis, jaundice, or both, with or without fever, may occur usually within the first one to three months of therapy. Determinations of liver function should be considered whenever unexplained fever, rash or other dermatologic reactions, or constitutional symptoms develop; if unexplained fever or other evidence of hypersensitivity occurs, discontinue CLINORIL. Elevated temperature and abnormalities in liver function caused by CLINORIL characteristically have reverted to normal after discontinuation of therapy. CLINORIL should not be reinstituted in such patients.

Hepatic Effects: In addition to hypersensitivity reactions involving the liver, in some patients the findings are consistent with those of cholestatic hepatitis. As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests without any other signs and symptoms may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with CLINORIL. Although such reactions as described above are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CLINORIL should be discontinued. In clinical trials, the use of 600 mg/day has been associated with increased incidence of mild liver test abnormalities (maximum recommended dosage is 400 mg per day).

Precautions: ***General:*** Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS: *Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy*). Although the effect on platelet function and bleeding time is less than with aspirin, CLINORIL is an inhibitor of platelet function; therefore, patients who may be adversely affected should be carefully observed when CLINORIL is administered. Pancreatitis has been reported (see ADVERSE REACTIONS); should pancreatitis be suspected, the drug should be discontinued and not restarted, supportive medical therapy instituted, and the patient monitored closely with appropriate laboratory studies (e.g., serum and urine amylase, amylase/creatinine clearance ratio, electrolytes, serum calcium, glucose, lipase, etc.); a search for other causes of pancreatitis as well as those conditions which mimic pancreatitis should be conducted. Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop eye complaints during treatment have ophthalmologic studies. In patients with poor liver function, delayed, elevated and prolonged circulating levels of the sulfide and sulfone metabolites may occur. Such patients should be monitored closely; a reduction of daily dosage may be required.

Edema has been observed in some patients taking CLINORIL. Therefore, as with other nonsteroidal anti-inflammatory drugs, CLINORIL should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention. CLINORIL may allow a reduction in dosage or the elimination of chronic corticosteroid therapy in some patients with rheumatoid arthritis. However, it is generally necessary to reduce corticosteroids gradually over several months in order to avoid an exacerbation of disease or signs and symptoms of adrenal insufficiency. Abrupt withdrawal of chronic corticosteroid treatment is generally not recommended even when patients have had a serious complication of chronic corticosteroid therapy.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of sulindac to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, the administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. CLINORIL may affect renal function less than other NSAIDs in patients with chronic glomerular renal disease (see CLINICAL PHARMACOLOGY section of Prescribing Information). Until these observations are better understood and clarified, however, and because renal adverse experiences have been reported with CLINORIL (see ADVERSE REACTIONS), caution should be exercised when administering the drug to patients with conditions associated with increased risk of the effects of nonsteroidal anti-inflammatory drugs on renal function, such as those with renal or hepatic dysfunction, diabetes mellitus, complications associated with advanced age, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. Since sulindac is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation. Since sulindac metabolites have been reported rarely as a component of renal stones, patients with a history of renal lithiasis should be given CLINORIL® (Sulindac, MSD) with caution and be kept well hydrated.

Information for Patients: CLINORIL, like other drugs of its class, is not free of side effects and can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis but also may be commonly employed for less serious conditions. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly in less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Use in Pregnancy: Not recommended for use in pregnant women, since safety for use has not been established and because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus) during the third trimester of pregnancy.

Nursing Mothers: Nursing should not be undertaken while a patient is on CLINORIL. It is not known whether sulindac is secreted in human milk; however, it is secreted in the milk of lactating rats.

Use in Children: Safety and effectiveness in children have not been established.

Drug Interactions: DMSO should not be used with sulindac; concomitant administration has been reported to reduce plasma levels of active sulfide metabolite and potentially reduce efficacy and to cause peripheral neuropathy. Although sulindac and its sulfide metabolite are highly bound to protein, studies with daily doses of 400 mg have shown no clinically significant interaction with oral anticoagulants or oral hypoglycemic agents; however, patients should be monitored carefully until it is certain that no change in their anticoagulant or hypoglycemic dosage is required. Special attention should be paid to patients taking higher doses than those recommended and to patients with renal impairment or other metabolic defects that might increase sulindac blood levels. Concomitant administration of aspirin significantly depressed the plasma levels of the active sulfide metabolite. Although addition of aspirin did not alter the types of clinical or laboratory adverse experiences, the combination showed an increase in the incidence of gastrointestinal adverse experiences; since addition of aspirin did not have a favorable therapeutic effect, the combination is not recommended. Concomitant administration of diflunisal in normal volunteers resulted in lowering of plasma levels of active sulindac sulfide metabolite by approximately one-third. Probenecid given concomitantly had only a slight effect on plasma sulfide levels, while plasma levels of sulindac and sulfone were increased; sulindac produced a modest reduction in the uricosuric action of probenecid, which probably is not significant under most circumstances. Neither propoxyphene hydrochloride nor acetaminophen had any effect on the plasma levels of sulindac or its sulfide metabolite.

Adverse Reactions: The following adverse reactions were reported in clinical trials or have been reported since the drug was marketed. The probability exists of a causal relationship between CLINORIL and these adverse reactions. The adverse reactions which have been observed in clinical trials encompass observations in 1,865 patients, including 232 observed for at least 48 weeks.

Incidence Greater than 1%: *Gastrointestinal*—Gastrointestinal pain (10%), dyspepsia,* nausea* with or without vomiting, diarrhea,* constipation,* flatulence, anorexia, gastrointestinal cramps. *Dermatologic*—Rash,* pruritus. *Central Nervous System*—Dizziness,* headache,* nervousness. *Special Senses*—Tinnitus. *Miscellaneous*—Edema (see PRECAUTIONS).

Incidence Less than 1%: *Gastrointestinal*—Gastritis, gastroenteritis, or colitis; peptic ulcer; gastrointestinal bleeding; GI perforation; liver function abnormalities; jaundice, sometimes with fever; cholestasis; hepatitis; pancreatitis (see PRECAUTIONS); ageusia; glossitis; a single report of sulindac metabolites in common bile duct "sludge" in a patient with symptoms of cholecystitis who underwent a cholecystectomy. *Dermatologic*—Stomatitis, sore or dry mucous membranes, alopecia, photosensitivity, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis. *Cardiovascular*—Congestive heart failure, especially in patients with marginal cardiac function; palpitation; hypertension. *Hematologic*—Thrombocytopenia; ecchymosis; purpura; leukopenia; agranulocytosis; neutropenia; bone marrow depression, including aplastic anemia; hemolytic anemia; increased prothrombin time in patients on oral anticoagulants (see PRECAUTIONS). *Genitourinary*—Urine discoloration; vaginal bleeding; hematuria; proteinuria; crystalluria; renal impairment, including renal failure; interstitial nephritis; nephrotic syndrome; renal calculi containing sulindac metabolites have been observed rarely. *Metabolic*—Hyperkalemia. *Psychiatric*—Depression; psychic disturbances, including acute psychosis. *Nervous System*—Vertigo, insomnia, somnolence, paresthesia, convulsions, syncope, aseptic meningitis. *Special Senses*—Blurred vision, visual disturbances, decreased hearing, metallic or bitter taste. *Respiratory*—Epistaxis. *Hypersensitivity Reactions*—Anaphylaxis, angioneurotic edema, bronchial spasm, dyspnea, hypersensitivity vasculitis. A potentially fatal apparent hypersensitivity syndrome has been reported; this syndrome may include constitutional symptoms (fever, chills), cutaneous findings (rash or other dermatologic reactions—see above), involvement of major organs (changes in liver function, jaundice, pancreatitis, pneumonitis with or without pleural effusion, leukopenia, eosinophilia, disseminated intravascular coagulation, anemia, renal impairment, including renal failure), and other less specific findings (adenitis, arthralgia, myalgia, fatigue, malaise, hypotension, chest pain, tachycardia).

Causal Relationship Unknown: Other reactions have been reported in clinical trials or since the drug was marketed but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians. *Cardiovascular*—Arrhythmia. *Metabolic*—Hyperglycemia. *Nervous System*—Neuritis. *Special Senses*—Disturbances of the retina and its vasculature. *Miscellaneous*—Gynecomastia.

Dosage and Administration: CLINORIL should be administered orally twice a day with food. The maximum dosage is 400 mg per day; dosages above 400 mg per day are not recommended. In osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, the recommended starting dosage is 150 mg twice a day; the dosage may be lowered or raised depending on the response. A prompt response (within one week) can be expected in about one half of patients with osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis; others may require longer to respond. In acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis) and acute gouty arthritis, the recommended dosage is 200 mg twice a day; after a satisfactory response has been achieved, the dosage may be reduced according to the response. In acute painful shoulder, therapy for 7-14 days is usually adequate. In acute gouty arthritis, therapy for 7 days is usually adequate.

Management of Overdosage: Overdosage has been reported, and rarely deaths have occurred. In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Animal studies show that absorption is decreased by the prompt administration of activated charcoal and excretion is enhanced by alkalinization of the urine.

How Supplied: Tablets CLINORIL containing 150 mg or 200 mg sulindac, with cellulose, magnesium stearate, and starch as inactive ingredients, in unit-of-use bottles of 60 and 100, unit-dose packages of 100, and bottles of 100.

*Incidence between 3% and 9%. (Those reactions occurring in less than 3% of patients are unmarked.)

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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CONTINUING MEDICAL EDUCATION

(Continued from Page 532)

June 23-24—**Certification Update for Radiographers.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

July 20-22—**General Surgical Postgraduate Course.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

July 17-20—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Ruidoso. Contact: Anne Woodrow, NM Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

September 7-9—**Concepts and Controversies in Perinatal Care.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 9-10—**First American Cancer Society Interdisciplinary Cancer Conference.** Bishop's Lodge, Santa Fe. Contact: Stephanie Gooch, American Cancer Society, NM Chapter, 5800 Lomas NE, Albuquerque 87110. (505) 262-2336.

September 15-16—**Essentials of Health Care for the Elderly.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 15-16—**New Mexico Chapter, American College of Surgeons—Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: NM Chapter, ACS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

September 22-23—**Southwestern Psychiatric Symposium on Schizophrenia and Depression.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

October 12-14—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 8-10—**13th Annual Spring Medical Symposium** (Sponsor: CH). Thurs-Sat. Radison Inn, Price. Contact: Max Morgan, MD, (801) 637-4800, ext 203.

June 18-23—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 12-14—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Salt Lake City. Contact: Barbara Saffel, (801) 466-3500.

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon. Jackson Hole, Wyoming. Contact: Midge Beckman, (801) 581-7480.

July 20—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

September 28-29—**Laser Surgery: General Surgery ND: YAG, CO** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

October 12-13—**Laser Surgery: Gastroenterology ND: YAG** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 540)

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069.

May 17—**Neurology.** Tacoma. Wed. Contact: (206) 627-7137.

May 18-19—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

May 20—**AIDS Education.** Everett. Sat. Contact: U/W (206) 543-3910.

June 1-2—**Nicotine Addiction.** Seattle. Thurs-Fri. Contact: U/W.

June 1-2—**Practical Management of Drug, Alcohol, and Tobacco Abuse Problems Within the Primary Care Population.** Seattle. Thurs-Fri. Contact: U/W.

June 1-3—**International Symposium on Pediatric NeuroOncology.** Seattle. Thurs-Sat. Contact: U/W.

June 2—**Current Otology.** Seattle. Fri. Contact: VMMC.

June 8-10—**Burn Update.** Seattle. Thurs-Sat. Contact: U/W.

June 9—**Ortho Trauma Update.** Spokane. Fri. Contact: U/W.

June 16-18—**Pediatrics Update.** Oregon. Fri-Sun. Contact: U/W.

June 26-27—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: (206) 627-7137.

June 28-30—**Comparative Implants for Orthopaedics.** Seattle. Wed-Fri. Contact: U/W.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349.

August 7-12——**Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

September 11-15—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 8-10—**Wyoming Medical Society—Annual Meeting.** Teton Lodge, Jackson. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009.

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Contact: Midge Beckman, (801) 581-7480. ◆

DYAZIDE®
25 mg. Hydrochlorothiazide/50 mg. Triamterene/SKF

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

Indications and Usage: Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.

Warnings: Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.

Supplied: Capsules containing 25 mg. hydrochlorothiazide and 50 mg. triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ:L58

** Ad Hoc Committee on Cardiovascular/Pulmonary Disease Risk Factors in Minority Populations: 1986 Forum on Cardiovascular Disease Risk Factors in Minority Populations. Bethesda, Maryland. U.S. Department of Health and Human Services, 1986.*

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According to a national survey by the U.S. government, the majority of adult Hispanic male hypertensives remain untreated and uncontrolled,* their future at risk of cardiovascular complications. For over 20 years, 'Dyazide' has delivered the dependable blood pressure control that helps reduce cardiovascular risk... while its low side-effects profile, convenient once-daily dosing, and real economy all make compliance easy.
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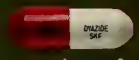
HELPS REDUCE CARDIOVASCULAR RISK.

Before prescribing, please see brief summary of prescribing information on adjacent page.



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Other Than Being Round: What Do the Eyes and the Testes Have In Common?

Marshall B. Block, M.D.

Having just completed a physical examination on a patient who I was following for a chronic medical problem, the patient turned to me and said, "Is that all you are going to do?" I was taken aback by the comment and wondered whether I had missed doing something that I should have perhaps performed. I thought back to this patient's history and realized that she had in the past seen multiple physicians at various high-powered multi-specialty clinics at various locations in the United States. Preventive medicine was very important to this patient and she had already had her life's maximum radiation exposure from numerous "routine" chest x-rays, barium enemas, upper GIs, and even CT scans.

It was, therefore, with some relief that an article appeared in the *Annals of Internal Medicine* (110:214-226;1989) which highlighted the uncertain significance of the routine physical examination in an asymptomatic patient. Not only was the value of the total examination brought into question, but the components of the examination were critically examined.

Over the past twenty years I had questioned the yield from examining the ears, nose and throat of my patients. It seemed to me that I found little significance in these routine maneuvers. It was, thus, gratifying that this article confirmed my feeling but little did I realize that other parts of the examination, similarly, lacked value. For instance, there is no data available for the utility of screening asymptomatic adults for lymphadenopathy. The yield does not warrant routine lymph node examination in asymptomatic patients. Likewise, the value of auscultation and percussion to detect lung problems is limited because of the large interobserver variability. According to this article, the lungs do not need to be percussed or to be auscultated as part of a physical examination in asymptomatic adults! So much for the thumping we performed on our spouses backs during medical school!

Screening for heart disease in asymptomatic individuals is a very controversial area. The American Heart Association recently recommended that an extensive cardiovascular examination be done at least every five years in healthy adults. However, the justification for these recommendations was not given nor is there any data to support such a conclusion. The contribution of the physical examination to the identification of early coronary artery disease has been studied only once and the results are not impressive. According to this article, a physical examination to screen for coronary artery disease is not a recommended procedure. What then should we be doing? Should every patient have a stress electrocardiogram? A thallium treadmill? Recent data suggests that even these studies are also fraught with false positive results.

How about the genitalia examination? There is no data to suggest that examination by a physician as a screening maneuver for the diagnosis of testicular cancer is useful. The article points out that self examination has been advocated but no studies have addressed whether such examinations are efficacious. The authors concluded that screening for testicular cancer cannot be recommended! Other than for telling me that I was going to go blind, my mother was right again about self examination of this area!

Perhaps an incident which occurred several years ago to my father brings physical diagnosis in perspective. I noticed that one of my father's eyes appeared smaller than the other. I immediately thought that some serious process was at play and suggested an ophthalmological evaluation. After an extensive examination, both by an ophthalmologist and a neurologist to whom he was laterally referred, he ultimately was told that there was no problem except that he was born with one eye that was smaller than the other! My father's response to me afterwards when I queried him about what had transpired was, "For this I send you to Medical School?"

The thing that keeps medical practitioners apart from other providers is our ability to objectively question our practices and unload obsolete behavior as new information appears. What then is science if not to question and test hypotheses, discarding those that are not fruitful?

Marshall B. Block, M.D., Editor

Journal of the Arizona Medical Association

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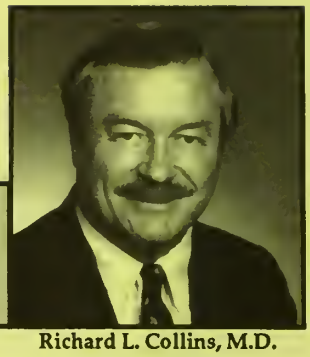
From Our President



Richard L. Collins, M.D.

One of the ongoing challenges to ArMA's legislative lobbying program each year are the bills filed which seek to limit the scope of physicians' authority to provide health care or to expand the scope of practice for allied health care providers.

We see examples this year in bills which would expand the scope of diagnosis and treatment by optometrists and which would allow naturopaths to be paid by insurance companies and have contracts with hospitals. ArMA is actively opposing both those bills and to date has been successful in stalling any action.

ArMA is also actively working for legislation that will correct existing limits on physicians' authority to practice or which will prevent such limits from being imposed. Examples are bills which would specify that physicians may dispense drugs and devices directly from their offices and which would authorize properly qualified physicians to supervise therapy aides.

ArMA successfully worked to amend legislation so that supervision of occupational therapy aides would not be restricted to licensed occupational therapists and so that a bill allowing patients to order their own lab tests now requires physician approval and notificaiton of lab test results.

ArMA has successfully opposed a bill which would have complicated the process of prescribing drugs so that it would be more difficiult to ensure dispensing of pharmaceuticals as ordered.

All of this legislation could affect the way you practice and the health care which your patients receive from others.

We believe it is our responsibility to let the legislature know the risks and responsibilities involved when nonmedical personnel are given the legal authority to perform procedures, therapies and other modalities which physicians alone have been professionally trained to do. We believe it is important to demonstrate that medicine as practiced by physicians should be the minimum standard acceptable, and that allied health providers should be required to meet the same standard before the scope of their practice is expanded.

To provide the legislature with factual information to use as a basis for decision-making, we spend much time and energy pointing out the problems involved when medical scope of practice is restricted or others' scope of practice is expanded.

There are political issues which come and go with the years, but protecting the quality of health care for Arizona's citizens is the heart of all our efforts in the legislature, every year.

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Planning Eliminates Problems

After a practice is formed, and its existence becomes assured, the physicians must plan to keep the practice alive through changes in ownership caused by the death or disability of one of the doctors. This is true of professional corporations as well as partnerships.

Most physicians realize the need to establish a buy/sell agreement, but too many have not entered into a formal written agreement, or adequately funded the buy/out as outlined in the agreement.

These agreements should provide for death, permanent disability, or temporary disability.

In the case of death. The buy/sell agreement addresses the current and projected value of the practice. A formula for determining the value of the practice should be spelled out in the agreement.

When planning for a corporation, the most common method is the stock redemption plan. The corporation owns life insurance policies on each doctor who is party to the agreement.

Upon the death of the insured, the corporation uses the life insurance proceeds to redeem the stock from the deceased doctor's estate, and the stock is retired as treasury stock.

A less common, but more attractive approach in smaller practices is the "cross-purchase" method. This involves each doctor owning a policy on his associate's lives, and using the proceeds to personally purchase shares from the estate of the deceased doctor. The advantages to this approach are that the survivor's basis in the practice are increased by the amount of shares purchased with income tax free insurance proceeds, *and,* the value of the practice isn't increased. This approach does not work too well where there are larger practices because of the multiplicity of policies required.

Each method should be examined to see what approach best fits, but they should always be funded with life insurance.

In the case of permanent disability.

Even though the chances of total disability are much higher than death during a physician's working years, many agreements do not take into account the possibility of this occurrence and fail to plan accordingly. The answer to this situation is the purchase of a disability buy/out policy which is available from several companies for the specific amount of the buy/out. The definition of disability in the agreement should parallel the terms of the disability policy. The buy/out policy pays the agreed-upon value of the practice. The physician's personal disability policy continues to provide income. Just recently, a major insurance company introduced a single policy, which addresses either death or disability, to fund buy/outs.

In the case of a temporary disability.

A real dilemma can be avoided when a doctor is temporarily disabled and unable to generate income which the practice needs to pay the overhead expenses. The use of business overhead insurance can be obtained with coverage provided for up to two years. This type of coverage can eliminate the disabled doctor's need to sell his portion of the practice while being temporarily disabled.

A well drafted buy/sell agreement, funded with insurance makes sense since it protects all of the parties involved.

ArMA Membership Benefits, Inc., represents many of the companies specializing in these types of coverage. We are experienced and objective in representing our member's needs in these matters.

Please call and we will be happy to explain in greater detail or will review your current planning with you.

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A sensible financial plan is one that eliminates taxes on your investment income--rather than just deferring taxes to a future time.

The equivalent yield table below illustrates the benefits of double tax exemption for individuals under 1988 federal tax rates and under current state tax rates. Locate your income tax bracket (after deductions and exemptions) and read across to see the approximate taxable yield needed to match the tax-free return of a **NUVEEN ARIZONA TRUST.**

For example, with joint taxable income of $29,800 to $71,900, you would be in the 32% combined federal and Arizona tax bracket and would need a taxable investment paying 10.66% to equal a tax-free return of 7.25%.

1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

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An Academic Heart Center Is Planned For Arizona

Despite a welcome downturn over the past decade in the incidence of death from myocardial infarction, diseases of the heart and blood vessels continue to represent the largest health care problem in the United States. Over 63 million Americans are estimated to have one or more forms of heart or blood vessel disease. Once considered diseases of the elderly, these disorders are now the primary cause of death among all individuals over 20 years of age. The younger age groups are by no means spared; an estimated 29,000 children are born each year with congenital heart disease. Many of these will live well into their adult years.

The health care system has responded to this challenge by the provision of increasingly sophisticated forms of treatment to progressively greater numbers of patients. Today the effects of most of the major forms of heart disease can be substantially ameliorated, but with the expenditure of enormous manpower resources and at a cost of billions of dollars annually.

The enormity of the problem and its steadily rising costs has created problems both for heart patients and their physicians. Faced with rapidly accelerating technological changes, cardiovascular physicians, like those in many fields, have become increasingly specialized. While this has improved the quality of care delivery, it has placed a variety of pressures upon the traditional organization of medicine into broadly defined departments. Cardiovascular specialists in medicine, surgery, and anesthesia now often feel that they have more in common with one another than with members of other subspecialties within their respective departments. On the other hand, departments organized along traditional lines are likely to remain in most institutions because of educational and accreditation requirements.

Particularly disconcerting to both patients and their physicians, is the accelerating costs of cardiac care. Many procedures once considered experimental, but now accepted as clinical practice, such as cardiac transplantation, are prohibitively expensive to large segments of the population. Within the next decade as artificial heart devices become more widely utilized, similar problems are likely to ensue.

A facile solution, often advocated by those comfortably removed from clinical decision making, is to limit access to high-technology interventions. Experience suggests, however, that financially motivated selection criteria are unlikely to achieve more than limited success and tend to disqualify the poor and elderly in disproportionate numbers.

A more promising solution, and one likely to favorably impact on the quality of care, equality of access, and costs, is a concerted effort to reduce the incidence of heart disease through research into its causes and methods of prevention. Considerable progress already has been made in a number of areas, including the identification of risk factors for coronary artery disease, the reduction in the incidence of rheumatic heart disease by the control of streptococcal infections and the development of safe, effective drugs for the management of hypertension.

Despite these accomplishments, much remains to be done. It cannot yet be said that we have a strategy in hand for the prevention of atherosclerotic or congenital heart disease. Ignorance abounds regarding the causes and methods of prevention of various cardiomyopathies, which together represent a significant proportion of patients under 50 years of age with end-stage heart failure.

Recent applications of biochemical and molecular techniques have lead to the discovery of the genetic basis for certain forms of inherited lipid disorders. These dramatic advances suggest that within the coming decades we will be able to deal with the root causes, and ultimately, develop methods of preventions for most heart and blood vessel diseases.

Against this background, the University of Arizona in Tucson has announced plans for a new Heart Center. The formal designation, University Heart Center, was chosen to emphasize its academic setting as part of the College of Medicine and its strong commitment to research and education. The center brings together research programs now scattered throughout various departments of the University which collectively command more than 24 million dollars in funding. Plans are being drawn up for a 100,000 square foot building to house new research laboratories. The building will adjoin expanded cardiovascular surgical facilities at University Medical Center.

A unique feature of the Center will be its effort to bring together researchers from basic sciences and clinical disciplines into highly integrated program areas. Major emphasis will be placed in the areas of cardiac embryogenies, the biochemistry of the myocardium, the epidemiology of heart disease, and the development of new strategies for the management of end-stage heart disease. The latter will include research on heart transplantation, for which the Center already is noted, and development of artificial heart devices. With its ambitious program, the new Center hopes to be a part of the solution to the problem of diseases of the heart and blood vessels and not a further contributor to the burgeoning costs of cardiac care.

Eugene Morkin, M.D.
Director, University Heart Center
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Physicians in the News

James F. Burke, M.D.

James F. Burke, M.D., was recently installed as president of the Arizona Academy of Family Physicians (AzAFP).

Dr. Burke was sworn in during the Academy's 40th Annual Scientific Assembly held February 23-26 at the Wyndham Paradise Valley Resort. The Assembly was attended by 242 physicians from 38 states. He was installed by James Jones, M.D., President, American Academy of Family Physicians.

Dr. Burke, a graduate of the Scottsdale Memorial Family Practice Residency Program, is currently president of the Scottsdale Memorial Hospital medical staff. He has been in private practice in Scottsdale since 1982.

David J. Gullen, M.D., has joined the board of trustees of The Flinn Foundation, Arizona's largest grantmaking organization, board chairman Donald K. Buffmire, M.D., announced today.

The addition of the long-time Arizonan expands the foundation's governing body to eight members.

Dr. Gullen joined Phoenix Medical Associates, a private medical practice specializing in internal medicine, in 1979. This year he was elected chairman of internal medicine at St. Joseph's Hospital and Medical Center, Phoenix. Gullen completed his undergraduate studies at Princeton University, received a master's degree in microbiology/immunology from Arizona State University, and earned his medical degree from U of A.

Dr. Gullen, who became board certified in geriatric medicine in 1988, is immediate past president of the Arizona Society of Internal Medicine and a member of the Arizona Medical Association.

The Flinn Foundation was established in 1965 by the late Dr. and Mrs. Robert S. Flinn with the broad mission of improving the quality of life in Arizona. The private, nonprofit foundation distributed more than $5 million in grants in 1988 in support of health care, education and the cultural arts.

Janice B. Dorn, M.D., Ph.D., of Phoenix, has passed the certification exam of the American Medical Society on Alcoholism and Other Drug Dependencies (AMSAODD) and is recognized by that society as knowledgeable and expert in chemical dependence.

Dr. Dorn is a member of the medical staff of Phoenix Camelback Hospital, and the Arizona Medical Association.

Five hundred forty-eight physicians throughout the country were certified this year by AMSAODD, the major national and international organization for physicians who aspecialize in addiction medicine. Including those certified in 1986 and 1987, there are now 1,823 AMSAODD-certified physicians.

The six-hour examination covers alcohol and all other addi ctive drugs, including nicotine, with questions equally divided between clinical issues and basic science. Recertification willl be required after 10 years in order for the certification to remain current.

NIA Grantees May Have Uncovered Key To Brain Pathology In Alzheimer's Disease

Two eminent neuroscientists have combined their research interests and uncovered a critical piece of information on why brain cells die in Alzheimer's disease.

Dr. Carl W. Cotman at the University of California at Irvine and Dr. Dennis J. Selkoe at Harvard Medical School and Brigham and Women's Hospital in Boston, Massachusetts, have found that a fragment of the protein in neuritic plaques may possess the ability to regulate growth of nerve cells in the healthy human brain.*

Neuritic plaques, which are dense, insoluble deposits of amyloid protein, are among the major pathological hallmarks of Alzheimer's disease. Until now, scientists have not known what role amyloid protein plays, if any, in healthy brain tissue or why an increasing number of large clusters of amyloid appear in the brains of Alzheimer patients.

Earlier NIA-supported studies revealed that the abnormal amyloid protein is made up of fragments of a larger protein that is normally spread across nerve cell membranes. Scientists also have discovered the approximate location of the gene for the fragment, called the amyloid precursor protein, and have identified the building block amino acids that constitute it.

In the current investigations, Drs. Cotman and Selkoe synthesized the first 28 amino acids of the amyloid protein and tested the effects of this synthetic peptide on nerve cells grown in tissue culture. Nerve cells grown in tissue culture do not survive long, but in the presence of the synthetic peptide, the cells stayed alive for longer periods of time. These results demonstrated that amyloid has a trophic, or growth enhancing effect on nerve cells.

On the basis of these experiments, Drs. Cotman and Selkoe speculate that plaque formation in Alzheimer's disease may signal the nerve cell's attempt to mount a defense against the degenerative process and to compensate for the damage that occurs as the disease progresses. The investigators also speculate that events in the early stages of Alzheimer's disease may lead to the production of an abnormal amyloid protein that malfunctions and contributes to the progress of the disease.

Scientists at the National Institute on Aging are hopeful about the results of this work, as well as recent research on nerve growth factor, one of several known trophic factors that enhances the survival of injured nerve cells. As investigators learn more about how and why cells die in Alzheimer's disease, it may become possible to slow the progression of the disease using nerve growth factor or similar substances.

Prior to this latest research, Dr. Selkoe was widely recognized for his research on amyloid protein as well as on the proteins that form the characteristic neurofibrillary tangles of Alzheimer's disease. Dr. Cotman distinguished himself with his pioneering studies of synaptic plasticity, the ability of damaged or diseased nerve cells to repair themselves. Both of the investigators have received long-term research support from the NIA and are recent recipients of NIA grants for Leadership and Excellence in Alzheimer's Disease (LEAD).

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*The results of this research, funded by the National Institute on Aging (NIA), appear in the March 17, 1989 issue of *Science* magazine, "Amyloid B Protein Enhances the Survival of Hippocampal Neurons *in Vitro*," by Janet S. Whitson, Dennis J. Selkoe, and Carl W. Cotman.

Guide To Patient Safety and Risk Management Programs Published

A comprehensive resource book, "Compendium of Patient Safety and Medical Risk Management Programs," has been published by the AMA/Specialty Society Medical Liability Project.

The book is the result of a study by the AMA and 32 national medical specialty societies and includes capsule descriptions of hundreds of programs and resources available to maintain and improve the quality of medical care.

This rapidly evolving field, known alternatively as patient safety, risk management, loss prevention and quality assurance, is covered to date in the 175-page, three-ring binder. Purchasers will receive periodic updates to ensure the volume's currency.

Resources and activities covered in the Compendium include: guidelines and policy statements adopted by medical organizations; courses and seminars; self-assessment programs; data banks; research projects; publications; audio-visual programs and listing of clearinghouses and resource centers.

The "Compendium of Patient Safety and Risk Management Programs" is available at $50 per copy from the AMA's Book and Pamphlet Fulfillment Dept. OP140, P.O. Box 10946, Chicago, IL 60610-0946 or by calling toll-free, 1-800-621-8335.

A limited number of review copies of the Compendiums are available to reporters. Please call Jane Coughlin, 312-645-4419, to request a copy.

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Arizona Medical Association 98th Annual Meeting

See details on page 14

Smoke-Free Class of 2000

The CIGNA Companies of Arizona have become the charter corporate sponsor of the "Smoke-Free Class of 2000" in Arizona. The project is designed to encourage the state's first-graders to graduate from high school in the year 2000 as non-smokers.

The educational project is a joint national effort by the American Cancer Society, the American Heart Association and the American Lung Association in response to U.S. Surgeon General C. Everett Koop's challenge to create a "smoke-free" society by the year 2000. The program is aimed at the three million children who began first grade last fall.

Research has shown that increasing numbers of children aged 10-12 are beginning to smoke. Cigarette smoking has not declined among high school seniors since 1984. Researchers say smoking will take the lives of more people than all other drugs combined.

There also appears to be a direct link between academic performance and smoking. In a recent study, only 7 percent of students reporting an average grade of "A" in high school were daily smokers, while nearly 50 percent of those averaging a "D" were daily smokers.

"We support this program because children are our future," said Clyde Wright, M.D., vice president and general manager of the CIGNA Companies of Arizona.

He continued, "If we begin teaching children that smoking is unhealthy in the first grade, and reinforce that message every year, we hope their knowledge and peer pressure will convince them not to smoke."

CIGNA's contribution will be used to pay for the first year of the program, which included a pledge to say "no" that children could sign, letters to their families to encourage support, five interactive story cards for use in the classroom, a song sheet with lyrics, stickers and posters. Children who "graduate" from the first grade will also receive a special certificate and a small gift.

Launched last September in Arizona, the program reached approximately 34,000 of the state's 56,000 first-graders this school year, according to coalition spokesman Frank Hubley.

"Obviously we hope to reach more children in this class in each successive grade," he said.

In addition to providing first-year funding, CIGNA is hoping to convince other Arizona companies to support the program, Dr. Wright said.

"It is our hope that other companies will join us to make it possible for our schools to teach the Class of 2001, 2002 and all children who follow, that smoking is not the thing to do," he explained.

C. Diane Bishop, state superintendent of public instruction, is honorary chairperson for the "Smoke-Free Class of 2000" in Arizona.

Mental Woes Can Profoundly Alter Sleep

By: J. Christian Gillin, M.D., Professor of Psychiatry, University of California, San Diego

In many ways, sleep is a mirror of moods. Sleep problems can be either the cause or the consequence of mental distress. Sleep difficulties can also appear together as core symptoms of a particular diagnosis such as depression.

In fact, one key indicator of good physical and mental health may be the absence of sleep problems.

Researchers exploring the biochemical relationship between sleep and mood suggest that changes in the body's internal clock may be at least partly responsible for some severe mood disturbances.

Insomnia Sufferers Display Altered Moods

The most recent major nationwide survey of sleep produced compelling findings about the relationship between sleep and mood.

Almost half the serious insomniacs were classified as having high degrees of mental stress. Most of the serious insomniacs with psychic distress displayed high levels of anxiety, and more than half had elevated scores on both anxiety and depression tests. High scores on both tests indicate that psychological symptoms were severe.

Serious insomniacs also were much more likely to report clusters of psychiatric symptoms that concur with diagnosis of a serious disorder. In particular, 21 percent of those with serious insomnia reported a pattern of symptoms that parallels major depression -- a prevalence more than three times higher than the percentage found among those with less marked insomnia.

Altogether, one-third of those with serious insomnia were characterized by syndromes resembling either major depression or generalized anxiety.

In addition, many patients with persistent insomnia suffer from other psychiatric conditions, such as obsessive-compulsive disorder, phobias or abuse of alcohol.

Is Sleep "Bad" for People With Depression?

Depression and sleep are intimately linked. Unipolar affective disorder -- a form of depression -- commonly includes symptoms of repeated awakenings and early morning wakefulness. Its sufferers also have less of the deepest phases of sleep (stages 3 and 4) than do people without depression and they dream earlier after falling asleep.

One night of total or partial sleep deprivation is known to alleviate depression. However, a night or less of recovery sleep usually restores depression in the patients who responded favorably to sleep deprivation. The treatment nevertheless provides valuable theoretical clues to the mechanisms of depression. While total cures for depression involving sleep deprivation therapy are rare, few other nonpharmacologic procedures work at all in so rapid a fashion. In fact, some investigators even believe sleep is "bad" for depressed patients.

Sleep deprivation therapy for the average patient appears to have little clinical usefulness at this time, but there is considerable hope that studying this phenomenon may help predict drug responsiveness or aid in developing prophylactic therapies.

Tricyclic antidepressants usually relieve insomnia, especially when sedating doses are administered at bedtime. Low doses of sedating antidepressants are sometimes given at bedtime to patients with chronic insomnia, while higher therapeutic doses may be given to treat both insomnia and depressed mood. The antidepressant effect may not be seen for several weeks. However, even after depression eases, many depressed patients continue to manifest sleep disturbances. Some doctors prescribe a sleep medicine with the antidepressants to deal with both concerns.

Panic Attacks Can Occur During The Night, Cause Insomnia

Persons with severe anxiety disorders also exhibit sleep impairment. The reports of insomnia in patients

with panic disorder -- a particularly severe form of anxiety -- may be related in part to a state of chronic physiological hyperarousal.

In a study of hospitalized panic disorder patients, all reported sleep disturbances, characterized by difficulty in falling asleep and multiple nocturnal awakenings. Although analysis of the patients' overnight sleep tracings were only partially consistent with their personal reports of broken sleep, patients with the highest ratings of anxiety and most frequent panic attacks did have the shortest total and least deep sleep.

Investigators have looked at the effects of one night's sleep deprivation on mood and behavior in panic patients. In contrast to the improvement shown by depressed patients, these patients did not get better. In fact, 40 percent experienced more anxiety and panic attacks on the day following sleep deprivation. These findings provide more evidence that panic and major depressive disorders have discernible biological underpinnings.

Circadian Rhythms, Mood and Sleep

For more than 30 years, clinical investigators have speculated that some or all of the symptoms of the depressive disorders, including manic-depressive illness, may be associated with abnormalities in the timing or phase control of the circadian system, the body's biological clock.

For example, many of the characteristic abnormalities of sleep in depression -- early morning awakening, short total sleep time and early appearance of dreaming -- are consistent with a "phase advance" of the circadian clock. That is, when a depressed patient goes to sleep at midnight, the body's internal regulating mechanisms look like those of a normal person at 6 a.m. In addition, there is some evidence that certain circadian rhythms, such as body temperature, have shallower peaks and valleys in patients with depression.

A class of medicine called benzodiazepines commonly prescribed for both sleep and anxiety disorders may affect the central circadian pacemaker. This pacemaker -- located in the area of the brain called the suprachiasmatic nucleus -- is the body's master clock. Recent research indicates that cells containing a brain chemical called gamma-aminobutyric acid (GABA) are present within this area. Benzodiazepines produce a calming effect by enhancing the action of GABA.

These specific biological associations between sleep and mood tell clinicians that it is important to look beyond the subjective complaint of insomnia for possible underlying causes. Treatments that solve both mood and sleep disturbances are available.

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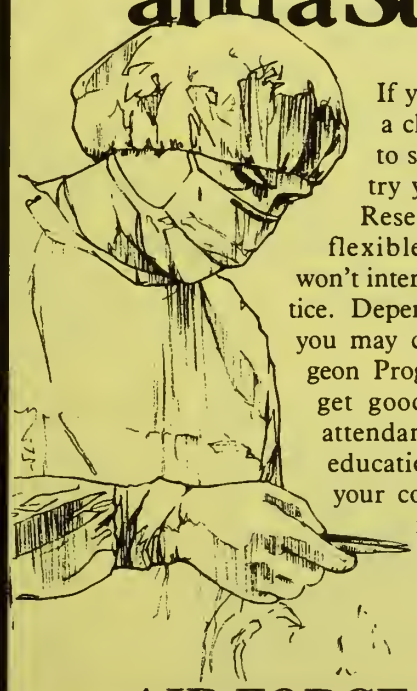

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SCHEDULE OF EVENTS

Thursday, June 1, 1989

8:00 a.m.-12:00 noon	**Current Perspectives Program**	
	Medicare & Third Party Payors	Section N
	High Tech Medicine	Section M
	Physician Office Laboratory Testing	Section O
	Exhibits & Breaks	Section K-L
8:30-10:00 a.m.	Auxiliary Opening Meeting	Section Q-R
10:00-11:-00 a.m.	Auxiliary Reference Committee	Section P
10:00-11:00 a.m.	Auxiliary Reference Committee	Section Q-R
11:00 a.m.-12 noon	Auxiliary House of Delegates	Section Q-R
12:00 noon-1:00 p.m.	Auxiliary Luncheon	Section G
1:00-5:00 p.m.	**Current Perspectives Program**	
	Political Education Program	Sections N-M
	Exhibits & Breaks	Sections K-L
7:00 p.m.	Reception	Hidden Valley
8:00 p.m.	Western Steakfry (casual)	Hidden Valley

Friday, June 2, 1989

6:00-8:00 a.m.	Executive Committee Breakfast	Section R
7:30-8:30 a.m.	Auxiliary County Caucus	Sections K-L
8:00-10:00 a.m.	Board of Directors	Sections M-N
8:30-10:00 a.m.	Auxiliary House of Delegates	Sections K-L
10:00 a.m.- 12 noon	House of Delegates	Sections A-B-E
12 noon-5:00 p.m.	Past Presidents' Luncheon	Etienne's DPOV
12 noon-2:00 p.m.	Joint Luncheon	Sections C-D
2:00-5:00 p.m.	Amendments Reference Committee	Section N
2:00-5:00 p.m.	Resolutions Reference Committee	Section M
2:00-5:00 p.m.	Auxiliary Summer Board Meeting	Sections K-L
7:00 p.m.	President's Reception	West Courtyard
8:00 p.m.	President's Banquet	Sections F-H

Saturday, June 3, 1989

6:30-8:00 a.m.	Maricopa County Caucus	Section K
6:30-8:00 a.m.	Pima County Caucus	Section L
6:30-8:00 a.m.	Rural County Caucus	Section M
8:00 a.m.-12 noon	House of Delegates	Sections A-B-E
12 noon-2:00 p.m.	Board of Directors	Sections M-N
12 noon-2:00 p.m.	Arizona Orthopaedic Society	Room 6001
12 noon-2:00 p.m.	Arizona Geriatric Society	Section I
1:30-3:30 p.m.	Hospital Medical Staff Section Program & Annual Meeting	Section L

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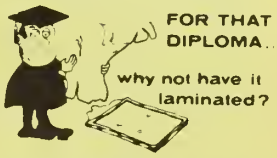

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Clinical Investigation

Chlamydia trachomatis and *Neisseria gonorrhoeae* in Asymptomatic Family Planning Patients in Rural New Mexico

THOMAS A. BELL, MD, MPH, *Seattle, and* MARJORIE R. EBENEZER, MD, MPH, *Maywood, Illinois*

We tested 98 asymptomatic women seen in state-funded contraception clinics in rural New Mexico. A fluorescein-conjugated monoclonal antibody stain revealed Chlamydia trachomatis *infection in 25% of asymptomatic unmarried women and 3% of married women (P = .03).* Neisseria gonorrhoeae *was detected in only one woman. As in urban clinics providing contraception, the prevalence of gonorrhea is rare in rural New Mexico, but chlamydial infections are common in young unmarried women.*

(Bell TA, Ebenezer MR: *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in asymptomatic family planning patients in rural New Mexico. West J Med 1989 May; 150:543-544)

Among women attending contraception clinics in urban areas, *Chlamydia trachomatis* infections are much more common than gonorrhea,[1,2] which is often considered to be an urban disease.[3] Less is known about the geography of genital chlamydial infections. They have been found in as many as 23% of Native Alaskan women[4] and 27.5% of pregnant Native Americans in New Mexico.[5] We know of no comparable data for rural women of European or Hispanic ancestry. Viable chlamydiae are difficult to transport from rural areas to central laboratories.[6] Direct staining of chlamydiae with monoclonal antibody stains permits the easier detection of chlamydial infections in remote clinics. We used this method to determine the prevalence of infection in women attending contraception clinics in rural New Mexico.

Subjects and Methods

Populations

From March through June 1987, we studied women in contraception clinics in Sandoval and Valencia counties. The clinics are run by the New Mexico Department of Health and the Environment, and more than 90% of the clientele have incomes below the federally defined poverty level. Subjects were recruited only if they were asymptomatic, 15 to 30 years old, had not taken antibiotics during the previous two weeks, and gave written consent.

Clinical Examination

Subjects were questioned about demographic characteristics and contraception. During the pelvic examination, the cervix was cleaned, and material for Papanicolaou smears and the direct detection of *C trachomatis* was removed. The identification of *Neisseria gonorrhoeae* was attempted with a Martin-Lewis medium.[7] Material for identifying *C trachomatis* was obtained with swabs pretested for their lack of toxicity (Micro Diagnostics, Medical Wire and Equipment Company [Bath] Ltd, Potley, Corsham, Wiltshire, United Kingdom). The *Chlamydia* transport medium was refrigerated and transported to the state laboratory in Albuquerque at the end of the work day and frozen at −70°C (−158°F).

Laboratory Methods

Smears for the direct detection of *C trachomatis* were stained and examined according to the manufacturer's directions (MicroTrak, Syva Diagnostics, Palo Alto, California).[8] Specimens were considered adequate for evaluation if the slide contained more than five columnar epithelial cells and the secretions were not too thick. They were considered positive if they contained five or more typical elementary bodies. Specimens for isolation (courtesy of W.E. Stamm, MD) were later shipped to Seattle, Washington, on dry ice.[9] Unfortunately, their temperature on arrival was 9°C to 12°C (48°F to 54°F).

Human Subjects

The study was approved by the Human Subjects Committee of the University of Washington and the Family Planning Review Board of the state of New Mexico.

Statistics

The χ^2 test and Fisher's exact test were used for comparisons of categorical data and Student's *t* test for continuous data. Confidence intervals (CI) were calculated with a microcomputer program, dEPID, version 2.1.[10]

Results

Consent was obtained from 124 subjects. Unevaluable specimens were obtained from 26 women (21%), whose demographic characteristics and contraception did not significantly differ from those of the other 98 women. The analysis is restricted to the remaining 98 women.

From the Department of Pediatrics and Epidemiology, University of Washington School of Public Health and Community Medicine, Seattle (Dr Bell), and the New Mexico Department of Health and the Environment, Albuquerque (Dr Ebenezer). Dr Ebenezer is currently with the Cook County Department of Public Health, Maywood, Illinois.

This work was supported by US Public Health Service grants Nos. EY-00219 and AI-12192.

Reprint requests to Thomas A. Bell, MD, MPH, Department of Epidemiology, SC-36, University of Washington School of Public Health and Community Medicine, Seattle, WA 98195.

The mean age of the 98 women was 22.0 years. The proportion currently married was 35%. The ethnic distribution was 65% Hispanic, 33% European ancestry and culture (Anglo), and 1% each of African ancestry (black) and Native American.

Chlamydiae were identified in 14 (14.3%) (95% CI, 7.6% to 21.2%) of the 98 evaluable smears and were isolated from 6 (43%) of the 14 specimens from women with positive smears but from none whose smears were negative. *N gonorrhoeae* organisms were isolated from 1 of 96 subjects tested; her smear was negative for *C trachomatis.*

Risk Factors for C trachomatis

The prevalence of chlamydial infection did not significantly differ between Anglo and Hispanic women—22% versus 11% ($P=.2$); between women using oral contraceptives or no contraception (14/89) and those using foam or condoms (0/9) ($P=.35$); or by age. The prevalence was 25% (95% CI, 10.4% to 30.1%) among single, divorced, or separated women and 3% (95% CI, 0% to 8.6%) among married women ($P=.03$).

Discussion

In rural New Mexico, genital chlamydial infection is common in asymptomatic poor, young, unmarried women seen in contraception clinics, while gonorrhea is rare. The prevalence of chlamydial infection that we found is lower than that in pregnant Native Americans in New Mexico[5] and higher than that in comparable clinics in the San Francisco Bay Area, California,[1] and in Seattle.[2]

In 1986, the rates of reported gonorrhea in Valencia and Sandoval counties ranked 14th and 18th, respectively, among New Mexico's 33 counties—59 and 55 per 100,000. In our study, chlamydial infection was 14 times more common than gonorrhea and is probably widespread in most other counties in New Mexico and perhaps much of the Southwest. The logistics of diagnosing these infections are problematic because testing for *C trachomatis* is impractical for rural health departments.

This and other such studies[1,2] have not given consistent results for risk factors for chlamydial infection. The rarity of gonorrhea in our population precludes its use as a proxy for chlamydial infection. The only way to effectively detect and treat chlamydial infection in such populations is to test for it specifically, especially in unmarried women.

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Clinical Medicine

Wound Site as a Predictor of Complications Following Deep Nail Punctures to the Foot

MICHAEL J. PATZAKIS, MD; JEANETTE WILKINS, MD; WILLIAM W. BRIEN, MD; *and* VINCENT S. CARTER, MD, *Los Angeles*

The site of injury, condition of the nail, and type of foot covering were compared in 36 inpatients and 34 outpatients with nail puncture wounds to the foot. Of the 36 inpatients, 34 (94%) had pyarthrosis, osteomyelitis, or both. The plantar surface of the foot was divided into 3 zones. Of the 36 inpatients, 35 (97%) had deep puncture wounds in zone 1. In contrast, only 6 of 34 (18%) outpatients had injury to this area. Tennis shoes were shown to predispose to infection with Pseudomonas aeruginosa. *Based on our findings, an early hospital admission should be considered for all patients with deep puncture wounds located in zone 1 and for patients who give a history of bone penetration in zone 2 or 3 at the time of injury. All patients who meet the above criteria and who are not admitted to hospital should be observed closely.*

(Patzakis MJ, Wilkins J, Brien WW, et al: Wound site as a predictor of complications following deep nail punctures to the foot. West J Med 1989 May; 150:545-547)

Nail puncture wound to the foot is a common injury that occurs at all ages. Numerous reports have been published that deal with the cause, diagnosis, management, and morbidity of infections following nail puncture wounds of the foot.[1-21] These reports have analyzed primarily patients who have required admission to hospital. Fitzgerald and Cowan reported on 869 patients with nail puncture wounds.[6] Of the 774 patients who were seen within 24 hours, 65 (8.4%) returned within four days with infection. Osteomyelitis developed in 14 (1.6%). Houston and co-workers evaluated 2,583 deep puncture wounds that included 280 (10.8%) cases with established infection when first seen. Of 2,303 "fresh" cases, infection subsequently developed in 51 (2.2%).

There are no reports to our knowledge that give criteria for hospital admission in the absence of disease following deep nail puncture wounds of the foot. We compare the sites of puncture, condition of the nail, and the foot covering in 36 inpatients with those of 34 outpatients who did not require hospital admission but who were evaluated after the injury at the Los Angeles County-University of Southern California (LAC/USC) Medical Center.

Patients and Methods

Inpatients

From July 1980 through September 1987, 36 patients were admitted to the Orthopaedic Infection Service or the Pediatric Pavilion at the LAC/USC Medical Center for infection following nail puncture wounds of the foot; 32 were male. Ages ranged from 4 to 59 years (median, 22), with 15 patients younger than 15 years and 21 adults older than 18. Three fourths of the patients (27) had medical attention before admission. Of these, 25 received an oral antibiotic either alone or after a single intramuscular injection of a cephalosporin. The time from injury to hospital admission ranged from 1 to 30 days (median, 9 days); 15 patients (42%) were admitted 14 or more days after the injury.

Outpatients

By reviewing outpatient medical records of daily visits, we identified 34 patients during 1986 and 1987 who did not require hospital admission following nail puncture wound to the foot; 29 were male. Ages ranged from 2 to 62 years (median, 28 years), with 9 patients younger than and 25 older than 18 years of age. Nearly 62% (21) of the patients were seen on the day of injury. Only three patients did not seek medical attention within 72 hours following the injury. We saw no seasonal pattern to the occurrence of this type of injury.

Results

Of the 36 inpatients, 2 had soft tissue infection involving a web space of the foot. The diagnosis and site of infection for the 34 inpatients with bone or joint involvement (or both) are given in Table 1. Combined pyarthrosis and osteomyelitis occurred in 19 patients, 11 had pyarthrosis, and 4 had osteomyelitis.

We divided the foot into three zones to determine if the site of puncture wound influenced the need for subsequent hospital care (Figure 1). Zone 1 encompasses the area that overlies the metatarsal neck region and extends distally to the end of the toes. Zone 2 extends from the distal end of the calcaneus to the neck of the metatarsals and overlies all of the tarsal bones and joints and the shaft of the metatarsals. Zone 3 overlies the calcaneus. We compared the zone location for nail wounds in the 36 inpatients and 34 outpatients. In 35

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inpatients, the nail puncture site was located in zone 1, with one found in zone 3 and none in zone 2. This can be contrasted to the location of the puncture site in the 34 outpatients, wherein 6 were located in zone 1, 23 in zone 2, 4 in zone 3, and 1 was not described. Tenting of the skin in the web space as described in one patient assigned to zone 1 pointed to involvement of the soft tissue only.

The type of foot covering and the condition of the penetrating nail are given in Tables 2 and 3, respectively. Of the 18 patients from both groups known to be wearing tennis shoes at the time of injury, 14 (78%) required admission to hospital. Of the inpatients in whom foot covering was known, 14/17 (82%) were wearing tennis shoes at the time of injury. The condition of the nail did not influence the need for hospital stay. It is of interest that *Pseudomonas aeruginosa* was grown from cultures of specimens from 13 of the 14 inpatients who were wearing tennis shoes; 1 had no growth.

Discussion

The incidence of serious complications has been reported to be 3% to 10% following a nail puncture wound to the foot.[1,6] This points to a need to identify those patients at risk for complications so that earlier definitive treatment can be given to decrease morbidity. We divided the plantar surface of the foot into three zones and looked for a difference in the site of injury to persons who were or were not admitted to hospital. Our data showed that puncture wounds in zone 1 were at the highest risk for the subsequent development of osteomyelitis, pyarthrosis, or both, followed by those of zone 3.

The data of previous investigators offer support to our observation that nail puncture wounds in zone 1 are at the highest risk for complications, followed by zone 3. Of 81 reported cases of osteomyelitis or pyarthrosis following a nail puncture wound to the plantar area of the foot, we were able to place 58 wounds into our zone classification.[2-5,7,9-12,14,16,19-21] Of the 58 wounds, 29 (50%) were in zone 1, 10 (17%) were in zone 2, and 19 (33%) in zone 3. Of the 23 cases not adequately described, 13 were reported to involve a metatarsus. The greatest risk for joint or bone penetration by a nail puncture in zone 1 can be attributed to the small amount of overlying soft tissue and by the fact that the metatarsal heads are a primary weight-bearing area of the foot. Conversely, the metatarsal arch and abundant soft tissue pad offer protection against bone or joint penetration from puncture wounds in zone 2. Its occurrence in zone 2 would more likely result from a puncture to the lateral rather than the medial aspect of the foot. Although the calcaneus is covered by the greatest amount of soft tissue, it is at risk for penetration by being a major weight-bearing area of the foot. Of 34 of our inpatient population, however, only 1 (2.9%) compared with 19/58 (33%) of previously reported cases had calcaneal osteomyelitis. The uncommon occurrence of calcaneal osteomyelitis following nail puncture wound may have influenced the reporting of cases.[3,13]

P aeruginosa is recognized as the most common infecting

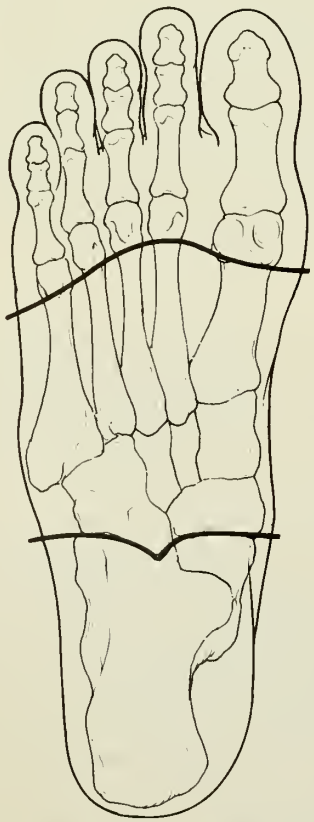

Figure 1.—The drawing shows the zones of the plantar surface of the foot.

TABLE 1.—*Type and Location of Infection in 34* Inpatients With Bone, or Joint Involvement or Both*

Location	Type of Infection: Pyarthrosis, No.	Osteomyelitis, No.	Combined, No.
MTP Joints			
1st	8	1	5
2nd	1	0	6
3rd	1	1	3
4th	1	0	4
5th	0	0	1
PIP Joint			
1st	0	1	0
Calcaneus	0	1	0

MTP=metatarsophalangeal, PIP=proximal interphalangeal

*Excluded 2 soft tissue infections.

TABLE 2.—*Type of Foot Covering*

Foot Covering	Inpatient, No.	Outpatient, No.
Tennis shoe	14	4
Shoe	2	8
Barefoot	1	2
Not known	19	20
Total	36	34

TABLE 3.—*Condition of Nail*

Nail Condition	Inpatient, No.	Outpatient, No.
Clean	5	8
Rusty	12	14
Dirty	1	2
Unknown	1	0
Not described	17	10
Total	36	34

organism following nail puncture wound to the foot.* Our findings further support that the wearing of tennis shoes at the time of nail puncture to the foot predisposes to infection with *P aeruginosa* in all age groups. We, unlike Minnefor and colleagues,[4] found no seasonal peak incidence of *P aeruginosa* osteomyelitis.

Conclusion

Based on our findings, hospital admission at the time of the initial medical evaluation of early deep puncture wounds of the foot, in the absence of clinical infection, should be considered for patients with wounds located in zone 1 and for patients who give a history of bone puncture in zone 2 or 3 at the time of injury. All patients who meet the above criteria and who are not admitted to hospital should be observed closely. Antibiotics chosen for patients wearing tennis shoes at the time of injury should have activity against *P aeruginosa.*

*References 2, 4, 5, 7, 10, 11, 13, 14-18, 21.

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Prevalence of Gestational Diabetes in a Navajo Indian Community

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A retrospective analysis of 4,094 deliveries among Navajo Indian women was carried out to determine the prevalence of gestational diabetes mellitus and diabetes antedating pregnancy. Three data sources—a local prenatal registry, a delivery room log, and hospital discharge records—were evaluated for their usefulness as surveillance systems for gestational diabetes. In all, 177 cases of gestational diabetes and 13 cases of preexisting diabetes were identified, giving a prevalence of maternal diabetes in pregnancy of 4.6%. When women with preexisting diabetes or documented gestational diabetes during a previous pregnancy were excluded, the prevalence of gestational diabetes during the study period was 3.4%. Although each data source used separately failed to identify 20% to 40% of diabetic pregnancies, more than 97% of cases were identified using a combination of the prenatal registry and the delivery log.

(Sugarman JR: Prevalence of gestational diabetes in a Navajo Indian community. West J Med 1989 May; 150:548-551)

The prevalence of non-insulin-dependent diabetes mellitus (NIDDM) is rising among many American Indian tribes.[1] If the hypothesis is correct that gestational diabetes mellitus represents the discovery during pregnancy of preexisting glucose intolerance rather than a separate disorder with a cause related to pregnancy,[2] then American Indian populations with high rates of NIDDM would be expected to have high rates of gestational diabetes when compared with the general population. This expectation is realized among the Pima Indians, who have the highest reported prevalence of NIDDM; the reported prevalence of abnormal glucose tolerance in Pima pregnancies is approximately 10%.[3,4]

Although the outcomes of diabetic pregnancies have improved considerably in the past half century, gestational diabetes still represents a risk factor for adverse perinatal outcomes.[3,5-7] In addition to its effects on perinatal morbidity and mortality, maternal diabetes in pregnancy is a powerful risk factor for the development of NIDDM in the offspring. The prevalence of NIDDM among the offspring of pregnancies complicated by diabetes in Pima Indians is 45% at ages 20 to 24, compared with 8.6% among the offspring of women in whom diabetes developed after the pregnancy.[8]

The age- and sex-adjusted prevalence of NIDDM among adult Navajo Indians, the largest Indian tribe in the United States, is about 60% higher than that in the general US population.[9] Because of the association of high rates of NIDDM with high rates of gestational diabetes in populations, and because of the clinical significance of maternal diabetes complicating pregnancy, a retrospective analysis of a large cohort of Navajo Indians seeking prenatal care at an Indian Health Service facility on the Navajo Reservation was done to determine the prevalence of gestational diabetes and NIDDM antedating pregnancy among pregnant Navajo women. In addition, three data sources were evaluated to assess their suitability as surveillance systems for gestational diabetes.

Patients and Methods

Shiprock Hospital is a 50-bed Indian Health Service hospital in northwest New Mexico located in the northeastern corner of the 25,000-square mile Navajo Reservation. There are about 40,000 registered patients at the facility, which has a catchment area of more than 4,000 square miles. Almost all Indian Health Service beneficiaries residing within the service unit are full-heritage Navajo Indians. Obstetric care is provided by obstetrician-gynecologists, certified nurse-midwives, and family practitioners.

All cases of Navajo women with gestational diabetes or preexisting NIDDM who sought prenatal care at Shiprock Hospital or who delivered at the facility and whose delivery dates were between October 1, 1983, and September 30, 1987, were identified by reviewing three sources of data. The first source is a registry of all prenatal patients receiving care at the Maternal Child Health Clinic at the facility. The registry entry for a patient is updated at each visit, and each case of gestational diabetes or preexisting diabetes is identified by a color-coded registry card. The prenatal and hospital records of all patients on the registry who delivered during the study period and in whom diabetes was diagnosed were reviewed to confirm the diagnosis of diabetes mellitus using criteria that will be discussed. All patients who delivered within the study period were included in the analysis, regardless of whether they delivered at the facility or elsewhere.

The second source, a delivery log, is maintained in the labor and delivery suite, and an entry is made for each parturient. The log includes a section of check boxes in which antepartum risk factors, including diabetes mellitus, are

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noted. All entries during the study period were reviewed, and those in which the box for diabetes was checked were added to the analyses after the diagnosis was confirmed by the chart review.

The final source is a list of all hospital discharges with ICD-9* codes 648.0 (diabetes mellitus complicating pregnancy, childbirth, or the puerperium) and 648.8 (abnormal glucose tolerance complicating pregnancy, childbirth, or the puerperium) for patients treated at Shiprock Hospital. The list was provided by the Indian Health Service Office of Program Statistics and was used to identify cases of diabetes from the first two data sets that were not so identified in the registry or the delivery log. Hospital and prenatal records were reviewed to confirm diagnoses, and all patients for whom one of the above codes was listed and who delivered during the study period were included in the analysis.

The criteria used by Indian Health Service providers for diagnosing gestational diabetes are detailed in Table 1. A policy that all patients seen in the clinic undergo screening for diabetes mellitus was instituted nine months before the study period. The clinic policy regarding screening frequency and criteria for gestational diabetes and the oral glucose tolerance test criteria for the diagnosis of gestational diabetes changed during the study period, and no attempt was made to standardize the diagnoses using one set of criteria. Clinical diagnoses of NIDDM were accepted if they met the National Diabetes Data Group criteria.[10] The 95% confidence intervals for prevalence figures were calculated using the binomial distribution.

Deliveries at Shiprock Hospital were numbered chronologically, and a random number generator was used to choose a sample of 100 patients. The sample was reviewed to establish the frequency with which screening blood glucose tests and follow-up oral glucose tolerance tests were done in the study population and to search for patients meeting the criteria for gestational diabetes but not included in one of the three data sets described above. The distribution of glucose screening by trimester was also recorded.

*International Classification of Diseases, ninth revision. Ann Arbor, Mich, Commission on Professional and Hospital Activities, 1978.

Results

A total of 177 cases of gestational diabetes and 13 cases of NIDDM antedating pregnancy were identified among 4,094 deliveries, yielding an overall prevalence of maternal diabetes in pregnancy of 4.6% (95% CI 4.0 to 5.3). When cases with preexisting diabetes or documented gestational diabetes during a previous pregnancy were excluded, the prevalence of gestational diabetes during the study period was 3.4% (95% CI 2.9 to 4.0). The rates for each fiscal year (October 1 to September 30) are detailed in Table 2. Eleven women contributed two diabetic pregnancies during the study period. All but three of the women in the study resided in the Shiprock Service Unit or in communities surrounding the service unit or sought prenatal care at Shiprock Hospital.

Patients with gestational diabetes were older (mean, 30.5 years; SD, 5.7 years) than were other obstetrical patients (mean, 24.9 years; SD, 5.8 years).

Of the randomly selected sample of prenatal patients, 90% had definite documentation of screening for gestational diabetes in the chart. Of the other ten patients, four had no prenatal care, three received prenatal care elsewhere and may have been screened, two received care elsewhere and were not screened, and one received care at Shiprock Hos-

TABLE 1.—*Screening and Oral Glucose Tolerance (OGT) Test Criteria for Gestational Diabetes, Shiprock (NM) Hospital, October 1, 1983, to September 30, 1987*

Time Period During Which Criteria Used	Screening Glucose Value 1 h After 50-gram Glucose Load, mg/dl	Oral Glucose Tolerance Criteria*				Schedule for Screening and OGT Test
		Fasting Blood Glucose Level, mg/dl	Serum Glucose Level After 100-gram Glucose Load, mg/dl			
			1h	2h	3h	
10/1/83 to 5/1/86	≥130	110	200	150	130	All screened at first visit; high-risk† women screened at 28 to 34 weeks' gestation
5/1/86 to 7/15/86	≥130	110	200	150	130	All screened at first visit and 28 to 34 weeks (if first visit at 24 to 28 weeks, screened at first visit and 32 weeks)
7/16/86 to 8/15/86	≥130	105	190	165	145	All screened at first visit and 28 to 32 weeks
8/16/86 to 9/30/87	≥140	105	190	165	145	All screened at first visit and 28 to 32 weeks

*Diagnosis of gestational diabetes mellitus made when any 2 OGT values are exceeded.
†High risk is a woman with a previous infant weighing 4 kg (9 lb) or more, a previous history of gestational diabetes, a family history of diabetes, suspected macrosomia, glucosuria, a previous unexplained stillborn, or a history of congenital anomalies.

TABLE 2.—*Prevalence of Gestational Diabetes Mellitus (GDM) and Preexisting Maternal Diabetes Among Navajo Indian Women Who Delivered From October 1, 1983, to September 30, 1987, Shiprock (NM) Hospital*

Date	Total Number of Deliveries	Cases With GDM or Preexisting Diabetes, No.	Prevalence of Deliveries With GDM or Preexisting Diabetes, %*	Documented GDM With Previous Pregnancy, No.	Preexisting Maternal Diabetes (NIDDM), No.	Prevalence of Deliveries With GDM Excluding Women With Previous GDM and Preexisting NIDDM, %*
10/1/83 to 9/30/84	992	41	4.1 (3.0-5.5)	7	5	3.0 (2.0-4.2)
10/1/84 to 9/30/85	1,041	35	3.4 (2.4-4.6)	7	1	2.6 (1.8-3.7)
10/1/85 to 9/30/86	1,005	67	6.7 (5.2-8.3)	13	4	5.1 (3.8-6.6)
10/1/86 to 9/30/87	1,056	47	4.5 (3.3-5.8)	12	3	3.1 (2.1-4.3)
Total	4,094	190	4.6 (4.0-5.3)	39	13	3.4 (2.9-4.0)

NIDDM=non-insulin-dependent diabetes mellitus

*Numbers in parentheses are 95% confidence intervals.

TABLE 3.—*Sensitivity (Percent) of a Series of Surveillance Systems for Identifying Gestational Diabetes and Preexisting Maternal Diabetes Among Navajo Indian Women Who Delivered From October 1, 1983, to September 30, 1987, Shiprock (NM) Hospital*

Delivery Date	Hospital Discharge Data,* %	Delivery Log, %	Prenatal Registry, %	Log or Registry, %
10/1/83 to 9/30/84	61	69	78	100
10/1/84 to 9/30/85	69	69	94	97
10/1/85 to 9/30/86	52	54	88	96
10/1/86 to 9/30/87	62	72	60	98
Total	61	64	80	97

*Data provided by the Indian Health Service Office of Program Statistics.

pital but failed to keep her scheduled appointment for screening. In all, 17 patients were screened only in the first trimester. Oral glucose tolerance tests were done in 75% (12/16) of those with screening results of 140 mg per dl or higher and 67% (14/21) of those with screening results 130 mg per dl or higher. All of the four patients with gestational diabetes noted in the random sample were included in one of the data sets. The diagnosis of gestational diabetes would have been made in one additional patient near the end of the study had the criteria for oral glucose test results for the early part of the study been applied.

The completeness of data sources for the surveillance of gestational diabetes varied. All three sources were highly specific, with only one patient on the maternal hospital discharge records and one patient on the prenatal registry incorrectly recorded as having gestational diabetes. (The patient on the prenatal registry had diabetes with a previous pregnancy but normal oral glucose tolerance during the index pregnancy.) The sensitivity of each data source—the number of cases identified on data source versus the total number of cases—is presented in Table 3. The combination of delivery log and prenatal registry identified the greatest number of cases.

Discussion

There has been little uniformity in the criteria used in studies attempting to estimate rates of gestational diabetes mellitus. Among several large studies in which the diagnosis was made on the basis of the results of one-hour 50-gram glucose screens and three-hour oral glucose tolerance tests, the prevalence of abnormal glucose tolerance in pregnancy ranged from 2.4% to 6.3%.[2] The prevalence of gestational diabetes in a small cohort of Navajo women at two Indian Health Service hospitals was 6.1%, although only 40% of Navajo women delivering at those hospitals during the study period were included in the analysis.[11] When 21 patients excluded from analysis in that study because a glucose screen was done before 28 weeks' gestation are included in the study denominator—thereby more closely reflecting the population in the present study—the prevalence of gestational diabetes in that study falls to 5.4%.

The prevalence of gestational diabetes is probably underestimated in the present study. About a quarter of patients with abnormal results on glucose screens did not undergo an oral glucose tolerance test in the random sample of the study population, primarily because patients failed to keep scheduled appointments. Because the positive predictive value of an abnormal screen in the random sample was 20%, the prevalence of gestational diabetes would have increased 1.4% if the rate of the disorder in the seven people without a definitive diagnosis was equal to that in the rest of the study population. In addition, 17% of the patients were tested only in the first trimester, and additional cases may have been diagnosed had all patients been screened in the second or third trimester. Furthermore, the clinical criteria for gestational diabetes used by local Indian Health Service providers changed during the study period, and it is possible that additional cases may have been diagnosed earlier in the study had the criteria of O'Sullivan and Mahan been used throughout the study period.[12] This may account for the greater number of cases diagnosed during the last two years of the study. In the random sample, however, one additional case that was not classified as gestational diabetes by the O'Sullivan and Mahan criteria would have met the criteria used earlier in the study. Finally, it is likely that a greater number of cases would have been diagnosed later in the study had the screening criteria of greater than 130 mg per dl been retained.

The study population included women who sought prenatal care at Shiprock Hospital or who delivered at the facility during the study period. While 98.4% of patients with diabetes resided either in the Shiprock Service Unit or in communities surrounding the service unit, or sought prenatal care at the facility, it is probable that some women living within the geographic boundaries of the service unit sought prenatal care and delivered elsewhere. No data system exists that would make it possible to determine whether women who resided in the service unit but who sought prenatal care elsewhere differed with respect to the prevalence of gestational diabetes of preexisting NIDDM from those included in the study population. It is unlikely that Navajo women with gestational diabetes or preexisting NIDDM were selectively referred to Shiprock Hospital for delivery from other areas, as no specialized obstetric or neonatal services distinguish it from other facilities within a 160-km (100-mile) radius. The possibility, however, that women in the study cohort were not representative of Navajo women within the geographic catchment area of the hospital cannot be definitely excluded.

All three surveillance systems would have resulted in an incomplete ascertainment of cases had each been used in isolation. Although the gold standard for the diagnosis of gestational diabetes was inclusion in at least one of the surveillance systems, the inclusion in at least one of the data sets of all cases of the disorder identified in the random sample is consistent with the hypothesis that few additional cases would have been identified by other methods such as a vital record review. Vital records have been examined as sources of data regarding the incidence of diabetes in pregnancy. In the states of Washington and South Carolina, birth and fetal death certificates identified less than 75% and 40%, respectively, of cases of maternal hyperglycemia that were noted on the mothers' hospital charts.[13,14] The prevalence of diabetes of 28/1,000 deliveries identified by hospital discharge data in this population of Navajo women is fourfold that identified in deliveries in South Carolina in 1978 and threefold to tenfold that identified by hospital discharge records in several other studies reviewed by the National Diabetes Data Group.[6]

Maternal diabetes mellitus in pregnancy appears to be more common among Navajo Indians than among the general US population. Surveillance of gestational diabetes among Navajos is best done when several data sets are com-

bined. Comprehensive prenatal registries have been advocated by others as mechanisms to monitor rates and outcomes of pregnancy in diabetic women.[15] Such registries may be particularly useful among other populations, such as other Native American communities and Hispanic populations in some parts of the United States believed to have high rates of non-insulin-dependent diabetes mellitus and gestational diabetes.[1,16] Because prenatal registries similar to that described above are not currently used at most Navajo Area Indian Health Service hospitals, the optimal surveillance of gestational diabetes among Navajos would be facilitated by establishing registries at those facilities. Efforts to develop local prenatal registries are currently underway.

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Clinical Review

Review of Acute Severe Asthma

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Status asthmaticus in the 1980s is still occasionally a fatal disorder. Preventable causes appear to be common: failing to appreciate the severity of the illness and undertreatment, particularly with steroids. Thus, an objective data base, early treatment, and frequent reassessment are of paramount importance. Despite intensive therapeutic intervention, mechanical ventilation may be required. In managing the ventilator in these patients, efforts should be directed at minimizing peak airway pressures while vigorous conventional modalities are continued. The need to use mechanical ventilation does not imply that the course of the disease will worsen, and the long-term outlook generally is good. Thus, even a low mortality rate is troubling. Once the acute process has resolved, educating the patient and close follow-up are essential.

(Franklin PK: Review of acute severe asthma. West J Med 1989 May; 150:552-556)

Affecting 3% of the United States population, asthma is one of the most common chronic illnesses seen by clinicians.[1] Unfortunately, despite advances in the understanding of its pathophysiology and major advances in its therapy, this disease still constitutes a source of serious morbidity and death. Because asthma is a reversible process, generally with a good long-term prognosis, even a low mortality should be viewed as preventable. I describe the clinical characteristics of severe asthma and review conventional therapeutic modalities as well as management options for patients with refractory bronchospasm.

Mortality

A great deal has been written recently expressing concern over continuing fatalities due to acute severe asthma.[2-9] In Great Britain the rate of asthma-related deaths throughout the first part of the 20th century was stable until the 1960s when mortality inexplicably rose.[5] Rates have returned to baseline, but substantial mortality remains. New Zealand likewise has experienced an increase in the number of deaths due to asthma.[7] This increased number of asthma-related deaths was initially felt to be due to marketing and prescribing practices of β-agonist inhalers. There was concern that through a synergistic action with theophylline, the toxicity of these drugs was dramatically increased.[7,10] This does not explain, however, why mortality rates remain regional even though there are no longer important differences in drug availability worldwide. The results of a detailed assessment of various causes of asthma-related deaths suggest that avoidable factors are common.[4,10] Chief among these factors is an inability of patients or physicians to recognize the warning signs of an impending crisis due to severe asthma. It then becomes of great importance to stress the evaluation of a case of acute asthma so an optimal course of treatment can be mapped out.

Pathophysiology

Several factors contribute to the pronounced obstruction to airflow that is characteristic of severe asthma. The easily reversible bronchoconstriction of a mild asthma attack is associated with only a mild inflammatory reaction. With increasing severity, vasodilation leads to substantial bronchial mucosal edema. Submucosal tissues are also edematous, with engorged vessels and hypertrophied glands. The inflammatory process is marked by increased eosinophils—and, to a lesser extent, neutrophils—in the airways and bronchial walls along with increased mucous secretion. This process leads to plugging of the distal bronchioles with a thick gelatinous material.[11] At autopsy the lungs are uniformly hyperinflated and fail to collapse. With this extensive plugging, a patient's life is at greater risk because further bronchoconstriction can lead to complete airways obstruction. Physiologically as a consequence of this severe plugging, there is increased wasted ventilation, an increase in ventilation-perfusion mismatching, and an increase in the work of breathing. These processes eventually lead to hypoxemia, accompanied in the end by both a respiratory and a metabolic acidosis.[12]

Assessment

An accurate assessment of the severity of an asthmatic episode is crucial. Acute attacks account for nearly 1 million emergency department visits per year, most of which are treated on an outpatient basis.[13] As a consequence, a physician may become complacent and unattuned to the warning signs that would earmark a patient for admission. Attempts have been made to create an index that would identify more severely ill patients.[14] The use of such indices has not been widely adopted as prospective studies have failed to confirm their predictive accuracy.[15,16] Individualized objective and, to a lesser extent, subjective assessments are essential in determining the need for closer observation and more aggressive treatment.

Historically the most common complaint will be dyspnea. In contrast to the classic teaching, this more often is inspiratory rather than expiratory dyspnea.[17] Patients apparently are better than examining physicians, regardless of experience, at judging the severity of an asthma attack. Furthermore,

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in one second
PEEP = positive end-expiratory pressure

patients are fairly consistent in correlating subjective feelings of improvement with objectively measured values.[18] Conversely, a patient's estimate that his or her condition is worsening, especially after emergency department treatment, is a good indication for admission to hospital. Other key historical points that place patients in a higher risk group include present or previous steroid requirements, a previous hospital admission, previous intensive care treatment, and a history of mechanical ventilation for an asthmatic exacerbation. The failure of an outpatient treatment regimen that had previously been effective identifies a subgroup of patients with a greater degree of inflammation and plugging of the airways. Finally, patients with a gradual course of deterioration will generally be slower to respond to initial bronchodilator therapy.[19]

Several features of the physical examination can call attention to the severity of an attack, the seriousness of which may otherwise be overlooked. Tachycardia, with a heart rate of greater than 130 beats per minute, has been correlated with a forced expiratory volume in one second (FEV_1) of less than a liter. As the obstruction resolves, the pulse drops despite a continued use of sympathomimetics.[20] With severe obstruction, wide fluctuations in intrathoracic pressures throughout the respiratory cycle lead to pulsus paradoxus—an inspiratory drop in the systolic blood pressure of greater than 12 mm of mercury. Although a pulsus paradoxus may be absent in a case of severe obstruction, its presence correlates with an FEV_1 of less than 40% of predicted.[21,22] Although wheezing is considered a hallmark of asthma, its severity may not correlate with the severity of the attack. A "quiet chest" may portend a worsening ability to move air and thus can be an ominous sign.

The early clinical signs of fatiguing respiratory muscles include an increasing respiratory rate, respiratory alternans (alternation between abdominal and rib-cage breathing), and abdominal paradoxic breathing (a paradoxic inward motion during inspiration). Respiratory muscle fatigue occurs because of a progressive pathophysiologic course of events. Premature closure of narrowed airways during expiration leads to an increase in the end-expiratory lung volume. With hyperinflation, all of the inspiratory muscles are shorter than they should be at the start of inspiration. As a result, these muscles operate at a less than optimal segment of their force-length curve and more work is required to achieve a given level of ventilation.[23(p136)] As expected, a patient's sense of dyspnea increases proportionately to the increase in the respiratory muscle workload.[24] Respiratory muscle fatigue ensues with the development of tachypnea, discordant respiratory movements signaling an impending increase in the partial carbon dioxide pressure and overt respiratory failure.[25]

Although, as previously mentioned, patients are often able to estimate the degree of obstruction, it has also been found that some are more breathless than others for any given reduction in the FEV_1. This variation in breathlessness is maintained over a wide range of reductions in the FEV_1.[26] With this potential for error on the part of both patients and physicians, simple objective measurements are necessary and should be considered an extension of the physical examination during both the initial assessment and when quantitating a patient's response to therapy. To accomplish this, the FEV_1 and peak expiratory flow rate are most commonly used. Of these two, the peak expiratory flow rate is easier to determine because it requires only a short forced expiration similar to a cough after full inspiration. Severe obstruction is clearly present if the peak expiratory flow rate is less than 100 liters per minute before treatment or is less than 300 liters per minute after the initial treatment. The FEV_1 may be more difficult to measure in an acutely dyspneic patient. When obtainable, however, it is clear that an initial FEV_1 of less than 0.7 liters or a posttreatment value of less than 2.1 liters shows a need for aggressive therapy.[20]

Arterial blood gas measurements are useful in further quantifying the severity of an acute attack. The most commonly seen pattern in asthma of moderate severity is hypoxemia associated with respiratory alkalosis. Increased ventilatory drive arises primarily from increased afferent activity from the respiratory muscles in their struggle against the mechanical workload and from pulmonary irritant receptors of the vagus nerve.[24] As bronchospasm worsens, increasing the minute ventilation only results in small increases in alveolar ventilation. Because a hyperventilating person with asthma generally has a low P_{CO_2}, any P_{CO_2} of 40 mm of mercury or greater should be viewed with increasing concern. Once the FEV_1 drops below 25% of predicted, hypercapnia develops. Similarly but less consistently, there is a rough correlation between the partial arterial oxygen pressure and FEV_1, with hypoxemia substantially worsening when the FEV_1 falls below 40% of the predicted normal.[27]

During a severe asthma attack, a chest radiograph will show signs of hyperinflation—increased radiolucency, depressed diaphragms, and widened rib spaces—in as much as 55% of patients.[22] Less commonly, other abnormalities, such as pneumonia, pneumomediastinum, pneumothorax, or atelectasis from mucous plugging, may show a need for specific therapeutic intervention.[28]

The electrocardiogram in patients with severe acute asthma commonly shows a number of abnormalities including cor pulmonale, right ventricular strain, and right axis deviation. These changes have been correlated with the severity of the obstruction and alterations in the heart position due to hyperinflation.[29] The abnormalities usually lessen with bronchodilators and should not by themselves be considered a contraindication to sympathomimetic therapy.[22] Older patients, however, especially those with a history of heart disease, should be monitored to detect dysrhythmias.

Individually none of the aforementioned components of the history and physical examination are adequate for an accurate assessment. They must be taken in combination and then frequently reassessed. Failure to do so has been implicated as a preventable cause of death in patients with severe asthma.[4,6] With a complete data base, a rational treatment program can be started.

Initial Therapy

Pharmaceutical Measures

Several drugs are important for treating a severe asthma attack. The mechanisms of action of these medicines have been reviewed in great detail.[30-32] How these agents are used in a patient with an acute attack is highly variable and guided in large part by personal preference.

A classic approach is initially to administer a subcutaneous sympathomimetic, such as epinephrine or terbutaline sulfate, which is repeated if necessary. If satisfactory improvement is not achieved, intravenous aminophylline and an inhaled β-agonist, such as 0.3 ml metaproterenol sulfate, are administered, often concomitantly with steroids. If deterioration continues, a cholinergic agent such as atropine sulfate is given.

Although this regimen generally works reasonably well, recent data suggest that significant changes should be made in our initial approach to severe asthma. Fanta and coworkers have shown a notably better response to inhaled β-agonists than to subcutaneous epinephrine when given initially to a patient with severe obstruction.[33] Adding intravenous aminophylline to inhaled β-agonist therapy did not produce substantial improvement over the administration of the β-agonist alone. This finding supports those of previous studies showing a lack of added efficacy associated with an increased toxicity with the addition of aminophylline in the therapy for acute attacks.[10,34]

Although patients with asthma have been found to be less responsive to cholinergics than patients with chronic obstructive pulmonary disease,[35] combining nebulized ipratropium bromide with a sympathomimetic has been shown to be more efficacious than using either drug alone.[36] Furthermore, this can be done without clinically significant increases in side effects.[37,38] When it becomes available in the near future, nebulized ipratropium bromide, in combination with an inhaled β-agonist, may further improve our therapeutic approach to acutely ill persons with asthma.

Treating acute severe asthma with the use of corticosteroids is essential when patients do not respond readily to initial therapy. Several authors have suggested that an underuse of steroids has been a contributing factor in asthma mortality.[4,6,39,40] Statistically significant improvement usually occurs within an hour after administering the drug, with a peak effect occurring within seven to nine hours. As improvement may not be shown for as long as 36 hours in certain patients, it is best to initiate steroid therapy early.[13] Although the efficacy of the short-term use of corticosteroids has been shown,[41] recommendations for appropriate dosing have varied widely.[3,13,20,42,43] A study by Haskell and associates showed a significantly better response in the FEV_1 to the administration of high doses of methylprednisolone sodium succinate—125 mg given intravenously every six hours—than to low doses—either 15 mg or 40 mg given intravenously every six hours—with minimal side effects.[44] Once an acute process has subsided, the regimen can be converted to prednisone, 60 mg, and then tapered. The time of taper varies, however, with the cause and severity of the attack and must be tailored to each patient.

Supportive Measures

All severely ill asthmatic patients should be placed on oxygen therapy. Ventilation-perfusion alterations associated with severe obstruction commonly lead to hypoxemia.[27] Treatment with bronchodilators can transiently worsen the hypoxemia by a few millimeters of mercury by aggravating the $\dot{V}/\dot{Q}$ mismatching.[45] The hypoxemia is usually corrected using relatively low concentrations unless severe mucous impaction and secondary atelectasis are present. Oxygen flow rates should be guided by serial measurements of arterial blood gases.

Because of high insensible losses, dehydration is common. Fluid management is guided by principles used in other acutely ill patients. Greater caution—and at times invasive hemodynamic monitoring—is, of course, required with concomitant cardiovascular disease. If a patient requires mechanical ventilation, hypovolemia becomes even more dangerous because high inflation pressures cause a considerable decrease in venous return with subsequent hypotension.[46] Conversely, hypervolemia has never been shown to improve the clearance of pulmonary secretions and should also be avoided.[12,47]

The upper respiratory tract infections frequently associated with asthmatic flare-ups are more commonly viral than bacterial, so the routine use of antimicrobials in patients with acute asthma is to be discouraged.[48] Their administration is reserved for situations in which a combination of findings suggests a bacterial process—that is, an infiltrate on chest x-ray film, purulent sputum with bacteria on a Gram's stain, and leukocytosis.

Mechanical Ventilation

Despite extraordinary therapeutic efforts, a few patients will deteriorate so that mechanical ventilation becomes necessary. Various criteria for the need for intubation have been suggested,[49] but the decision must be tailored to individual cases. Often there is a fine line between giving the medication time to reach its maximal effect and continued deterioration so that intubation is done under less than optimal emergency conditions. Changes in mental state, however, and respiratory muscle fatigue with worsening respiratory acidosis generally indicate an inescapable need for mechanical ventilation. Although at times tempting, the use of sedatives must be avoided as these agents are a common iatrogenic cause of respiratory depression in already borderline patients.

Once the decision to intubate has been made, a nasotracheal approach is best after an adequate local application of lidocaine hydrochloride to the nasopharynx and larynx. This decreases patient discomfort and inhibits bronchospasm induced by irritating the larynx. This reflex, which is parasympathetically mediated, may be further inhibited with the administration of atropine.[12] A tube 8 mm or larger will minimize resistance and allow for more effective suctioning. Furthermore, if necessary, bronchoscopy may be more easily done through the larger tube.

After the airway has been secured, sedation with intravenous diazepam or morphine sulfate is needed. Although of questionable clinical significance,[11,47] morphine's potential to provoke histamine release is thought by many authors to make diazepam the drug of choice.[46,49,50]

Mechanically ventilated patients with asthma have an associated mortality rate of about 15%.[49] Complications in these patients occur at nearly three times the rate of those in patients ventilated for other reasons. This increase in morbidity and mortality is related to anoxic encephalopathy, cardiopulmonary failure, or pulmonary barotrauma as a result of extremely high pressures needed to overcome airway obstruction.[40,51,52]

Few clinical situations present as great a challenge to clinicians as mechanically ventilating an asthmatic patient. Several points may prove useful in the management of the ventilator. A volume-cycled ventilator should be used so that constant tidal volumes are maintained. Tidal volumes of 10 to

12 ml per kg body weight are delivered at a low ventilatory rate—that is, 8 to 12 breaths per minute. Caution is needed in adjusting the inspiratory-expiratory ratio. The increased expiratory time needed to prevent additional air trapping requires shortening the inspiratory time and using a higher inspiratory flow rate. Unfortunately, this increases peak airway pressures further. Sedation—and occasionally paralysis with pancuronium bromide—may be necessary to produce apnea. This allows for both a slower inspiratory flow and a longer expiratory time, which should aid in combating the high peak pressures and air trapping.[12] A paralyzed patient must be kept unaware by adequate sedation. Once a day the paralyzing medication should be stopped and consciousness restored so neurologic function can be assessed.

In an effort to minimize barotrauma, several authors suggest limiting peak inspiratory pressures to 50 to 55 cm of water.[51,53] If these levels are exceeded, adjustments in the tidal volume or inspiratory flow rate are made to lower the peak pressures. This may result in an inadequate minute volume with subsequent hypercapnia and respiratory acidosis. An elevated Pco_2 is accepted while the pH is corrected with an intravenous bicarbonate infusion. Critics of this approach point out the potential risk of posthypercapnic metabolic alkalosis.[49] Furthermore, the difference in central nervous system permeability between carbon dioxide and bicarbonate might result in continued central nervous system acidosis when the systemic pH was normal. This theoretically could produce alterations in the mental state.[53] Nevertheless, this combined strategy has been successful in lowering morbidity and mortality.[51]

The period of mechanical ventilation is usually brief, with an average duration of 61 hours.[47] During this time intense drug therapy is continued. Weaning cannot start until the airways obstruction has been adequately treated. This can be judged by a decrease in peak inspiratory pressures, a spontaneous negative inspiratory force of −30 cm of water, and a vital capacity of at least 15 ml per kg body weight.[12] In rare cases, the patient remains refractory despite conventional pharmaceutical therapy and mechanical ventilation. Under such circumstances, several other modalities can be considered.

Halothane

The general anesthetic halothane is a potent bronchodilator that neither stimulates respiratory secretions nor causes laryngeal irritation.[54] Despite halothane's potential benefits in asthmatic patients, its use is limited by side effects. Halothane readily produces circulatory depression, frequently with various arrhythmias because it is a strong negative inotrope.[55(p278)] Because of its narrow margin of safety, continuous bedside monitoring by an anesthesiologist is mandatory.

Bronchoscopy

As previously discussed, widespread tenacious plugging of the airways is an important feature in patients who die in status asthmaticus. Gross atelectasis, a common complication in these patients, may be caused by proximal mucous impactions. Removal of these plugs by fiber-optic bronchoscopy may improve ventilation.[13,52] There are anecdotal reports of successful bronchial lavage—generally with solutions that include acetylcysteine—to remove peripheral mucous plugging.[56-58] This procedure must be monitored closely, however, as it can initially worsen the patient's condition. Bronchoscopy has been associated with an increase in bronchospasm, an excess of respiratory tract infections, arrhythmias, and possibly pneumothorax.[39,59] In a deteriorating patient unable to tolerate bronchial lavage, extracorporeal membrane oxygenation support has been used to provide temporary support while serial bronchoscopies were successfully carried out.[59]

Positive End-Expiratory Pressure

The use of positive end-expiratory pressure (PEEP) has generally been considered to be contraindicated in asthma. It has been thought that PEEP increases an already high functional residual capacity and peak inflation pressures. However, high levels of PEEP have been reported to actually decrease peak airway pressures by "treating" the severe bronchospasm, with a subsequent improvement in patient status.[60]

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Medical Progress

Adult T-Cell Leukemia-Lymphoma

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Adult T-cell leukemia-lymphoma, an aggressive T-cell leukemia, is characterized by the presence in the peripheral blood of malignant T cells that have highly indented or lobulated nuclei. Phenotypically the cells are usually helper T cells, but functionally they behave as suppressor cells. Patients have skin and lung involvement, hepatosplenomegaly, moderate lymphadenopathy sparing the mediastinum, and various metabolic abnormalities such as hypercalcemia. The clinical course may be chronic or acute, usually followed by a rapidly progressive terminal course. Adult T-cell leukemia-lymphoma is now known to be caused by human T-cell lymphotropic virus type I, which has been identified in the cells of patients with the disease.

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Adult T-cell leukemia or adult T-cell leukemia-lymphoma (ATLL) is an aggressive T-cell leukemia that was first described in 1977 by Uchiyama and co-workers in a group of adult patients living in southwestern Japan.[1] It is characterized by the presence in the peripheral blood of malignant helper T cells that have highly indented or lobulated nuclei. Patients present with skin and lung involvement, hepatosplenomegaly, lymphadenopathy sparing the mediastinum, and hypercalcemia. The clinical course may be chronic or acute but is usually followed by a rapidly progressive terminal course. This unusual clinical syndrome is now known to be caused by human T-cell lymphotropic virus type I (HTLV-I), which has been identified in the cells of patients with ATLL.[2,3] I will review the epidemiologic and clinicopathologic features of ATLL and will discuss the current understanding of the way in which HTLV-I transforms human T cells.

Epidemiology

One of the most striking features of the original group of patients described by Uchiyama and associates was the geographic proximity of their birthplaces.[1] All of the patients lived in or around big cities on the island of Honshu in southwestern Japan at the time of the diagnosis of ATLL; 13 of 16 had been born and had grown up on Kyushu, 8 of them in the province of Kagoshima. To explain this unusual clustering of cases, a search for an oncogenic virus was undertaken. Working independently, Gallo and colleagues[2] and Hinuma and co-workers[3] isolated a unique type C retrovirus from patients with ATLL that they called HTLV-I. Gallo's group identified viral particles in an HUT-102 T-lymphoblastoid cell line from a patient originally thought to have aggressive cutaneous T-cell lymphoma but recognized in retrospect to have ATLL. Hinuma and associates identified the same retrovirus in an MT-1 cell line from a patient with ATLL.[3]

Since identification of HTLV-I, extensive seroepidemiologic surveys have shown that the virus exists not only in Japan, where it is the most common cause of leukemia-lymphoma,[4] but also in other parts of the world. It is now known to be endemic in the Caribbean, where it is associated with half the cases of T-cell leukemia-lymphoma,[4,5] central Africa, the Pacific basin, northeastern South America, and the southeastern United States.[6-9] Cases have also been identified in nonendemic regions such as Israel and Great Britain; in many of these cases, patients had immigrated from or traveled to an endemic area.[9-11]

Serum antibodies to HTLV-I are found not only in patients with ATLL but also in lower titers in healthy adults.[6,11,12] A large epidemiologic survey in Japan showed that the antibody was present in 6% to 37% of healthy adults living in endemic regions but only sporadically among those living in nonendemic regions.[11] Healthy relatives of patients with ATLL have an especially high incidence of seropositivity.[6,13,14] In one study, almost 50% of relatives of virus-positive Japanese ATLL patients were seropositive; in the United States and the West Indies, relatives had a three to four times incidence of seropositivity compared with the general population.[15]

Epidemiologic surveys such as these indicate that the virus is not widely distributed in the general population, a finding that can be explained at least partially by the mode of transmission of HTLV-I. The virus appears to be transmitted in one of three ways, each of which requires the passage of infected cells from one person to another.[8,16,17] These include the passage of infected semen from one partner to another during sexual intercourse; the passage of infected blood cells from person to person either through a blood transfusion or intravenous drug use; and passage from mother to fetus, possibly in breast milk or through the transplacental transmission of infected lymphocytes.[8,18-21]

Etiology

Evidence Implicating HTLV-I

The human T-cell lymphotropic virus type I was implicated as the agent responsible for ATLL when in vitro studies showed incorporation of its proviral sequences into the DNA

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ABBREVIATIONS USED IN TEXT

ATLL = adult T-cell leukemia-lymphoma
HTLV-I = human T-cell lymphotropic virus type 1
IL-2 = interleukin-2
LDH = lactic dehydrogenase

of host ATLL cells.[22] In addition, cocultivating HTLV-I-infected T cells and normal T cells resulted in a rapid transformation of normal cells.[10,23] The immortalized cell lines resembled primary tumor cells from ATLL patients morphologically as well as in other ways: they showed the potential for indefinite growth, had an increased number of interleukin-2 (IL-2) receptors, and showed a decreased requirement for IL-2.[4,10,14] Although the virus can infect cells other than T cells, it does not cause their transformation.[8]

Studies of patients with malignant disorders other than ATLL further support the association between HTLV-I and ATLL. A monoclonal or oligoclonal pattern of viral integration is seen in malignant ATLL cells but not in other types of malignant cells, showing that viral infection precedes expansion of the malignant ATLL clone.[8] In addition, the incidence of seropositivity among patients with other malignant tumors living in either endemic or nonendemic regions approximates that of other healthy adults in the same regions.[11,17] This suggests that the presence of anti-HTLV-I antibodies in patients with other malignant diseases is a coincidental finding.

Epidemiologic and in vitro evidence supports the concept that HTLV-I is acquired during life, rather than being inherited. First, the incidence of seropositivity increases with increasing age, reaching a maximum between ages 40 and 60[11]; the disease tends to affect older persons; and it develops in people who emigrate from endemic to nonendemic regions later in life.[9,24] Thus, infection by the virus appears to predate the emergence of malignancy. Second, HTLV-I proviral sequences are found in the DNA of neoplastic T cells but not in the DNA of nonneoplastic B cells from the same patient,[25] supporting the concept that HTLV-I is an exogenous virus acquired by infection and not by transmission in the germ line.

Despite the apparent role that HTLV-I plays in causing ATLL, infection with the virus alone apparently is not sufficient to cause the development of ATLL. It is estimated that as many as 98% to 99% of patients infected with HTLV-I never have any signs or symptoms of the disease, suggesting that another cofactor is necessary for the development of overt leukemia in infected persons.[8] The long latent period between infection and the development of disease, the variable rate of progression of the disease in infected persons, and the in vitro finding that the virus is only expressed in cells harvested from ATLL patients after they have been in culture all support the idea that a cofactor is necessary.[26] Because active infection is not required for the growth of ATLL cells, it is possible that HTLV-I is necessary for inducing leukemia but is not adequate for the maintenance and progression of the disease.[8,27]

The Virus and Mechanisms of Transformation

The mechanism by which HTLV-I causes the transformation of normal T cells is not fully understood. It is clear, however, that this virus is unique among known acute or chronic transforming retroviruses. First, it has no sequences that are homologous to known oncogenes.[28,29] In addition, it shows no preference for a specific site of integration into cellular DNA, the site varying from tumor to tumor.[30] Thus, HTLV-I does not cause a transformation of T cells by either insertional mutagenesis or viral oncogenesis.[4,29]

The structure of HTLV-I is similar to that of animal oncogenic retroviruses. It has a long terminal repeat at the 5′ and 3′ ends of the genome; a *gag* gene, which encodes the group-specific core proteins p19, p24, and p15; a *pol* gene, which encodes reverse transcriptase; and an *env* gene, which encodes envelope glycoproteins.[26,30-32] Unique to HTLV-I is a strongly conserved gene in the 3′ region, called the *x* gene, also known as *x-lor* or *tat* (transactivator gene of transcription).[28,29] The *x* gene encodes a protein of molecular weight 40,000 that is found in the nucleus of infected cells.[28] This *x* protein, when produced in even small amounts, stimulates *x* transcription and thus viral replication.[28,29,33-35] Not only is this protein essential for the efficient replication of the virus, but it also appears to be required both for the active infection of T cells and for their immortalization. It is possible that the *x* protein induces cell transformation by causing an abnormal transactivation of factors, such as interleukin-2, involved in regulating normal T-cell proliferation.[4,8,36]

Pathology

Cellular morphology in ATLL is highly variable. The most consistent feature is the presence in the peripheral blood of pleomorphic, medium to large lymphocytes with indented or polylobulated nuclei. The cytoplasm is scant, nuclear chromatin coarsely clumped, and nucleoli inconspicuous.[37-41]

Approximately 65% of patients have leukemia at the time of presentation; it will develop in essentially all of them at some time during the course of their illness.[42] At autopsy, the bone marrow is involved in 95% of patients, although the extent of involvement may be less than expected based on the peripheral blood abnormalities.[41]

Involvement of lymph nodes, except those in the mediastinum, is common in these patients; hence, the name adult T-cell leukemia-lymphoma. Because of notable pleomorphism in the pattern of involvement of nodes,[41] however, a biopsy may not be diagnostic; examining the peripheral blood is usually more productive. This heterogeneity may hinder categorizing the nodes according to lymphoma classification systems now in use. The lymphoma is usually classified as being one of the following: pleomorphic, large-cell immunoblastic, lymphoma of medium-sized cells, or lymphoma of mixed-cell type.[37,38]

A biopsy specimen of the skin in ATLL reveals dermal and subcutaneous infiltration by tumor cells; about two thirds of patients have focal epidermal infiltration by tumor cells that may resemble Pautrier's microabscesses seen in the Sézary syndrome.[37,39,42]

At autopsy, organs other than the bone marrow, skin, and lymph nodes are often involved. Hanaoka and colleagues found malignant cells in the adrenal gland in 90% of patients, in the lung in 70%, in the liver in 56%, in the kidney in 47%, in the gastrointestinal tract in 47%, and in the central nervous system in 25%.[41] Many organs also showed calcium deposition. Pulmonary lesions were especially prominent and were often the cause of death; these lesions included infiltration by tumor cells, interstitial pneumonia, bronchopneumonia, hemorrhage, strong exudation with hyaline membrane formation, or infection with opportunistic organisms such as

Pneumocystis carinii, cytomegalovirus, herpesvirus, *Nocardia*, *Candida*, and *Aspergillus*.

Chromosomes and Immunology

A variety of clonal chromosome abnormalities has been found in ATLL, but no single abnormality has been consistently associated with the disease. Among those described are trisomy 7 or 7q, 14q+, +3, 6q−, 5q−, 9q−, and loss of the X chromosome.[43-46] The meaning of the cytogenetic abnormalities in ATLL is unclear because viral integration into the cellular genome occurs randomly on different chromosomes in ATLL cells from different patients.[30] Despite this, the extent of chromosomal abnormalities appears to be related to the severity of disease; many abnormalities are seen in patients with acute disease, while few if any changes are seen in patients with chronic or smoldering disease,[47] implying that cytogenetic abnormalities may evolve as the disease progresses.

Immunologic Findings

The typical surface phenotype of ATLL cells is that of mature helper T cells: CD2+, CD3+, CD4+, CD8−, and CD25+.[36,46,48] CD25, which identifies the IL-2 receptor (Tac antigen), is five to ten times as high in ATLL cells as it is in normal activated T cells.[49] Despite their helper phenotype, these cells act as suppressor cells, inhibiting normal B-cell differentiation.[48] Variants of ATLL showing a suppressor phenotype have been described; cells from these patients, who differ from typical ATLL patients in having an extremely high lactic dehydrogenase (LDH) level, may have undergone phenotypic changes during the course of the disease due to an extremely high proliferative rate, thus resulting in the loss of some original surface markers.[48]

Clinical Features

Adult T-cell leukemia-lymphoma is a heterogeneous clinical disorder that can be divided broadly into four stages based on the extent of disease and the temporal course. These include preleukemia, smoldering ATLL, chronic ATLL, and prototypical subacute or acute ATLL.[8,22,50]

In the earliest or preleukemic stage of ATLL, patients have anti-HTLV-I antibodies but are asymptomatic. The diagnosis is made when examination of the peripheral blood in patients incidentally noted to have leukocytosis reveals the presence of typical morphologically abnormal lymphocytes. Disease is detectable in the bone marrow but in no other organs. About 50% of these patients have a long-lasting spontaneous regression of their disease occurring within months to years after the original diagnosis. The other half has persistence of the T lymphocytosis; some of them will progress to the acute (crisis) phase, which is rapidly fatal despite therapy.

A second group of patients has smoldering ATLL. This group was first recognized by Yamaguchi and co-workers, who described five seropositive patients living in endemic areas who differed from typical ATLL patients in that they presented with the gradual onset of skin lesions that flared up after years.[51] The duration of disease ranged from 22 to 156 months. Skin lesions variably consisted of erythema or papules or nodules associated with slight infiltration of the skin by ATLL cells. Other than the skin findings, the physical examination showed no abnormalities. The peripheral blood of these patients showed 0% to 2% ATLL cells, and the bone marrow showed only minimal involvement; the results of blood chemistry tests were normal. Two of five patients died despite therapy when their disease transformed to a more aggressive form resembling acute ATLL; this occurred in one patient 5 years after diagnosis and, in the other, 15 years after diagnosis.

Closely related to patients with smoldering ATLL is a third group with chronic ATLL.[50] These patients are distinguished from those having smoldering ATLL by the presence of a significant number of abnormal cells circulating in the peripheral blood. They, too, may progress after months to a more acute form of the disease that is fatal.

A fourth group of ATLL patients has a prototypical subacute or acute ATLL.[1,12,37,41,52-54] These patients frequently present with rapidly progressive skin lesions variably consisting of localized or generalized erythroderma, nodules, nonspecific plaques, papules, or patches. On physical examination, about 80% of patients have mild to moderate peripheral lymphadenopathy and about half have hepatosplenomegaly. Hilar and retroperitoneal nodes are involved in as much as 50% of cases, but, in contrast to other aggressive T-cell malignant diseases, mediastinal nodes are not involved. Involvement of the lung and leptomeninges is also typical. On laboratory examination, there is usually mild anemia, a leukocyte count that may range from 10 to several hundred $\times 10^9$ per liter,[51] hypercalcemia, an elevated LDH level, an increased alkaline phosphatase concentration, and hyperbilirubinemia.[37,51,53] Patients with typical ATLL may initially respond well to chemotherapy but generally relapse rapidly with resistant disease (see discussion of treatment).

Special Complications

In contrast to other types of non-Hodgkin's lymphoma in which hypercalcemia affects about 2% of patients,[55] hypercalcemia is a prominent complication of ATLL, estimated to occur in 26% to 100% of patients at some time in the course of their illness.[56] Symptoms of hypercalcemia may actually predate the diagnosis of ATLL by several months.[54] Abnormalities of calcium metabolism may exist even in normocalcemic patients.[56]

Patients present with typical symptoms of hypercalcemia, such as lethargy, constipation, confusion, dehydration, and polyuria.[37,54-57] The hypercalcemia may be unresponsive to treatment with standard measures until chemotherapy for ATLL is instituted. Not infrequently, hypercalcemia is associated with the terminal phase of the disease and may be a cause of early death.

The mechanism of hypercalcemia in ATLL is unclear. Laboratory studies in these patients show increased bone turnover and osteoclast activation, suggesting that ATLL cells produce a humoral factor that causes increased bone resorption. This factor has yet to be identified, but possibilities under investigation include a substance with osteoclast-activating factorlike activity,[54,55,57] transforming growth factor-β,[58] a parathyroid hormonelike substance,[52,54,56] and interleukin-1.[36]

Diagnosis

The diagnosis of ATLL should be suspected in adult patients with typical clinical features and circulating neoplastic cells with pleomorphic nuclear indentations or lobulations; confirmation requires the finding that the malignant cells have a mature helper T-cell phenotype and that anti-HTLV-I

antibodies or HTLV-I proviral DNA sequences are present.[22] Although most patients will be seropositive, it may be necessary in some patients to apply newer, more sensitive techniques, such as the polymerase chain reaction, to detect HTLV-I sequences.[59]

The major disorders that must be differentiated from ATLL include chronic lymphocytic leukemia, Sézary syndrome or mycosis fungoides, non-Hodgkin's lymphoma, and Hodgkin's disease.[59] These disorders can usually be ruled out on the basis of differences in their presenting features and clinical course, a lack of typical peripheral blood malignant cells, the absence of HTLV-I, differences in immunologic markers, and a lack of typical T-β-chain gene rearrangements.[60-62] The presence or absence of hypercalcemia, an elevated LDH level, or both may be helpful but not diagnostic.

Treatment and Outcome

The treatment of ATLL depends on the extent of the disease in a particular patient. In general, patients with preleukemic, smoldering, or chronic forms of ATLL need no treatment unless they progress to a more aggressive stage.[8] In contrast, patients who have subacute or acute forms should be treated immediately with aggressive chemotherapy or radiotherapy (or both). Various regimens have been tried.[1,5,6,37,52,54,63-65] Most patients respond rapidly to aggressive therapy, but remissions are short-lived. Patients relapse either in the area of the initial disease or elsewhere, such as the leptomeninges, within months. Salvage chemotherapy may be effective briefly, but, again, patients ultimately relapse and die of resistant disease. Mortality is about 50% in less than five months.[51] Treatment is made more difficult in these patients because of the frequent presence of metabolic abnormalities such as hypercalcemia and the high rate of infection with opportunistic infections.

Because of the generally dismal prognosis of patients with acute ATLL, several experimental approaches are under investigation. Some of these include using anti-Tac monoclonal antibodies to eliminate the IL-2 receptor-expressing cells[4]; using α-emitting isotopes or toxins conjugated to anti-Tac; and using azidothymidine or 2,3-dideoxycytidine to inhibit HTLV-I infectivity and replication.[15] These approaches and others need further evaluation to determine their usefulness in ATLL.

The ATLL patients with the worst prognosis appear to be those with the highest tumor burden, hypercalcemia, opportunistic infections, and spread to the leptomeninges.[37,52,66] A recent study showed that a poor performance status and high LDH values were the most reliable independent predictors of poor response and survival[67]; high LDH levels were also associated with worse disease-free survival. A specific pathologic subclassification was not an independent predictor of a poor prognosis. Two other recent studies[36,68] have shown that serum levels of soluble IL-2 receptors correlate with tumor burden and disease activity and may in the future be used to predict prognosis.

Summary

Adult T-cell leukemia-lymphoma is a heterogeneous disorder caused by the human T-cell lymphotropic virus type I and characterized by the presence of morphologically distinct pleomorphic helper T cells circulating in the peripheral blood. Since its first description in a group of Japanese patients, our understanding both of ATLL as a discrete disorder and of the ways in which viruses may be involved in causing malignancy has expanded tremendously. With the introduction of ever-evolving sophisticated molecular techniques, it is likely that in the not-too-distant future we will understand how HTLV-I causes ATLL and will be able to apply that knowledge to the study of other cancers.

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Medical Staff Conference

Management of Hypercholesterolemia
A Primary Care Perspective

Discussant
ROBERT B. BARON, MD, MS

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *The therapy for hypercholesterolemia and other hyperlipidemias is a major problem now facing the primary care physician and anyone else who is concerned about the treatment of impending or real vascular disease. We are fortunate to have Dr Robert Baron at this conference to discuss the subject of the management of hypercholesterolemia from the primary care perspective.*

ROBERT B. BARON, MD, MS†: The focus of this review will be recent developments and persistent controversies concerning the relationship of hypercholesterolemia to coronary artery disease and the development of a practical approach to patient management in primary care practice. Specifically, I will address five questions:

- Why treat hypercholesterolemia?
- Who should be screened?
- Who should be treated?
- Is diet therapy effective? and
- Have the magic bullets finally arrived for drug therapy?

Why Treat Hypercholesterolemia?

Our current belief that increased blood cholesterol levels, particularly increased low-density lipoprotein (LDL)-cholesterol levels, are strongly and causally related to coronary artery disease comes from the results of many epidemiologic studies. Clinical experience with patients with genetic hyperlipoproteinemia and laboratory evidence from various disciplines have further strengthened this belief. Yet, only in the past year, with the publication of the report of the National Cholesterol Education Program (NCEP) of the National Heart, Lung, and Blood Institute,[1] has an aggressive approach to detecting and treating hypercholesterolemia been strongly advocated. Five recent studies have provided sufficient additional evidence to justify such an approach.

The long-term follow-up study of 361,622 men screened for the Multiple Risk Factor Intervention Trial (MRFIT)[2] has greatly clarified the relationship between blood cholesterol levels and coronary artery disease. In this large cohort of middle-aged men, the average blood cholesterol value was about 5.2 mmol per liter (200 mg per dl). Cholesterol levels of 6.4 mmol per liter (245 mg per dl) were associated with a twofold greater risk of dying of coronary artery disease in six years. Cholesterol levels of 7.8 mmol per liter (300 mg per dl) doubled the risk again. Lower than average cholesterol levels were associated with a decreased risk. An even more striking observation from this study was the realization that the relationships between cholesterol, coronary artery disease mortality, and total mortality were virtually identical to the relationships between hypertension and the same clinical end points. This observation has strongly suggested that both our clinical and public health approaches to the management of these two risk factors should be similar.

The Lipid Research Clinic Coronary Primary Prevention Trial[3,4] was a randomized study of 3,806 men, aged 35 to 59 years, with total cholesterol levels of greater than 6.9 mmol per liter (265 mg per dl). Subjects were randomly assigned to receive a diet plus placebo or a diet plus cholestyramine and were observed for seven to ten years. Administering cholestyramine resulted in a 13% reduction in total cholesterol levels, a 20% reduction in LDL-cholesterol levels, and a 3% increase in high-density lipoprotein (HDL)-cholesterol levels. The number of definite coronary deaths decreased 21%, and all coronary end points decreased 17%. Total mortality rates were not reduced in the experimental group, however, due to an increase in noncardiovascular mortality rates, including suicides and accidents. This was the first large multicenter study to show a clear reduction in coronary artery disease mortality with lipid modification.

The Helsinki Heart Study was a randomized, double-blind, five-year comparison of the use of gemfibrizol and placebo in 4,081 men aged 40 to 55 years with non-HDL-cholesterol levels of more than 5.2 mmol per liter.[5] Using gemfibrizol caused an 8% reduction in total cholesterol levels, an 8% reduction in LDL-cholesterol values, a 35% reduction in triglyceride levels, and a 10% increase in HDL-cholesterol levels. A 34% decrease in the incidence of cardiac events was seen in the gemfibrizol-treated group. Although a 26% decrease in coronary artery disease mortality was also seen, this was not statistically significant. There was

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
LDL = low-density lipoprotein
NCEP = National Cholesterol Education Program

also no difference in total mortality. Analysis of the effects of the lipid alterations on coronary artery disease suggested that the changes in LDL- and HDL-cholesterol levels were strongly associated with the decline in the incidence of coronary artery disease while the reduction of triglyceride levels was not.[6] This was the first major clinical trial to show that raising the HDL-cholesterol levels results in a reduction in the coronary disease incidence.

The Cholesterol-Lowering Atherosclerosis Study randomly assigned 162 nonsmoking men aged 40 to 50 years with previous coronary artery bypass grafts to receive either diet therapy and placebo or a combined regimen of diet, colestipol hydrochloride, and nicotinic acid.[7] The combined treatment resulted in a 26% reduction in total cholesterol values, a 43% reduction in LDL-cholesterol levels, and a 37% increase in HDL-cholesterol levels. A blind assessment of angiograms showed a regression of atherosclerotic lesions in 16.2% of drug-treated subjects and 2.4% of placebo-treated subjects and fewer new lesions in both native vessels and grafts in drug-treated subjects. This was the first major clinical trial to show that aggressively reducing LDL-cholesterol levels can result in a regression of coronary atherosclerosis in some patients.

The Coronary Drug Project was a randomized trial conducted between 1966 and 1975 of 8,341 men aged 30 to 64 years with an electrocardiographically documented myocardial infarction at least three months before entry.[8] Subjects were randomly assigned to receive one of six regimens including low-dose estrogen, high-dose estrogen, dextrothyroxine sodium, clofibrate, nicotinic acid, and placebo. The initial three regimens were discontinued early in the study because of adverse events. At the end of the study, no efficacy was found for the use of clofibrate whereas nicotinic acid treatment showed a modest decrease in the incidence of nonfatal myocardial infarctions. No effect on total mortality was observed. Using nicotinic acid resulted in a 10% decrease in total cholesterol levels and a 26% decrease in triglycerides. A long-term follow-up of 6,000 men in 1984 showed that patients treated with nicotinic acid during the trial had an 11% decrease in subsequent total mortality rates.[9] This was the first major clinical trial to show that modifying blood lipids can result in a decrease in total mortality.

Despite this evidence, some authorities have questioned the cost-effectiveness of an aggressive cholesterol-lowering treatment program that requires frequent physician and dietician visits, medications, and laboratory tests.[10] A recent comparison of alternative strategies for managing coronary risk has clearly shown that a smoking-cessation program or even surgical treatment of left main coronary artery disease is more cost-effective than cholesterol-lowering treatments.[11] Determining the cost per year of life saved by reducing cholesterol levels largely depends on the medication chosen. Less expensive medications such as nicotinic acid or oat bran make cholesterol reduction more cost-effective than the treatment of moderate hypertension, whereas the use of expensive medications such as colestipol in individual packets is four times more expensive. These are difficult social issues that must be resolved on a societal level in the context of other health- and non-health-related costs.

Despite these controversies, the National Cholesterol Education Program has recently embarked on a nationwide effort to improve the detection, evaluation, and treatment of hypercholesterolemia in adults. The following remarks are largely based on the NCEP perspective.

Whom to Screen? Initial Classification by Total Cholesterol Levels

Each adult patient should have a total blood cholesterol level measured at least once every five years. Fasting before the specimen is drawn is not required. Despite the simplicity of this recommendation, the results of a recent survey by the Centers for Disease Control suggest that we still have a long way to go to meet this goal.[12] Only 47% of persons surveyed have ever had a blood cholesterol level measured, only 19% have ever been told their cholesterol level, and only 6% actually know their blood cholesterol level. Blood cholesterol levels can then be categorized as desirable (less than 5.20 mmol per liter [200 mg per dl]), borderline high (5.20 to 6.21 mmol per liter [200 to 239 mg per dl]), or high (6.24 mmol per liter [240 mg per dl] or higher). By dividing a continuous biologic variable into discrete categories, we are, by definition, creating arbitrary classifications. These levels have been chosen primarily because 6.24 mmol per liter is the 75th percentile of cholesterol levels in the United States and is the level at which the risk of dying of coronary artery disease doubles.

The initial follow-up is based on this categorization. Patients with desirable blood cholesterol levels can be reassured and advised to have their cholesterol levels rechecked in five years. It is important that such patients not become overly focused on their blood cholesterol, particularly at the expense of other preventive health measures. Patients with higher blood cholesterol levels need further management, as will be discussed.

The next step of classifying patients with borderline cholesterol levels is determined by the presence or absence of coronary artery disease or its risk factors. The other risk factors to consider are shown in Table 1. Male sex is considered a risk factor because of the higher incidence of coronary disease found in men at any given cholesterol level. A family history of premature heart disease is defined as a myocardial infarction or sudden death in a parent or sibling before age 55. Hypertension and diabetes mellitus are risk factors whether or not they are being treated. Smoking more than ten cigarettes per day, a history of stroke or peripheral vascular disease, obesity of greater than 30% overweight, and an

TABLE 1.—*Risk Factors for Coronary Artery Disease (CAD) Other Than Borderline Cholesterol Levels*

Male sex
Family history of premature CAD (definite MI or sudden death before age 55 in a parent or sibling)
Cigarette smoking (more than 10 cigarettes per day)
Hypertension
Low HDL-cholesterol (<0.9 mmol per liter [35 mg per dl])
Diabetes mellitus
History of definite cerebrovascular or occlusive peripheral vascular disease
Obesity (>30% over "desirable weight")

HDL=high-density lipoprotein, MI=myocardial infarction

HDL-cholesterol level of less than 0.91 mmol per liter (35 mg per dl) are also independent risk factors.

Although the multiplicative relationship between risk factors has been known for some time, this is the first time that a national policy recommendation for the management of one risk factor is affected by the presence of other risk factors. Patients with borderline cholesterol levels who do not have two or more risk factors are given dietary information and rechecked annually to screen for a further elevation of cholesterol levels, but an intensive intervention is not needed. Patients with borderline cholesterol levels who already have coronary artery disease or who have two or more other coronary risk factors require the determination of an LDL-cholesterol level, as will be described.

This emphasis on associated risk factors is based on the principle that the greater a persons's risk of having the disease being prevented, the greater the possible benefit from a preventive intervention. Table 2 shows a comparison of the risk of death from coronary artery disease per 1,000 men based on blood cholesterol values in two groups of men: hypertensive smokers and normotensive nonsmokers. Although the relative risk of coronary disease as a function of cholesterol elevation is approximately equivalent (6.4/1.6 versus 21.4/6.3), the absolute number of preventable deaths is greater in the high-risk group (15.1 versus 4.8).

Whom to Treat? Classification by LDL-Cholesterol Levels

All patients with high blood cholesterol levels (>6.24 mmol per liter) and those patients with borderline blood cholesterol levels (5.20 to 6.21 mmol per liter) who have either coronary artery disease or two or more other risk factors should be further evaluated by the determination of an LDL-cholesterol level. The LDL-cholesterol value is estimated from fasting measurements of serum lipids using the following equation: LDL-cholesterol = total cholesterol − (HDL-cholesterol) − (triglycerides/5). At least two LDL-cholesterol estimations should be done and averaged. Despite improved standardization of most large laboratories in the past year, there remain a 2% to 3% analytic variability and a 10% intraindividual biologic variability in cholesterol measurements.

Patients are then further categorized based on the LDL-cholesterol levels. Values of less than 3.38 mmol per liter (130 mg per dl) are desirable, and no further treatment is indicated. Those between 3.38 and 4.13 mmol per liter (130 and 159 mg per dl) are borderline; levels above 4.16 mmol per liter (160 mg per dl) are high. Patients with borderline or high LDL-cholesterol levels should be evaluated with a careful history and physical examination to rule out secondary causes of hypercholesterolemia and should be assessed for a genetic hyperlipidemia. The treatment of borderline and high LDL-cholesterol levels should then be initiated according to the guidelines shown in Table 3.

TABLE 2.—*Coronary Artery Disease Deaths Per 1,000 in Men Aged 35 to 37 Years With an Average Follow-up of 6 Years According to Serum Cholesterol Quintile and Presence or Absence of Other Risk Factors**

Serum Cholesterol Quintile, mmol/liter (mg/dl)	*Normotensive Nonsmoker*	*Hypertensive Smoker*
<4.73 (182)	1.6	6.3
4.73-5.25 (182-202)	2.5	10.3
5.28-5.72 (203-220)	2.7	15.5
5.75-6.34 (221-244)	3.8	16.6
>6.37 (245)	6.4	21.4

*From Martin et al.[2]

TABLE 3.—*Indications for Treatment Based on LDL-Cholesterol Levels*

	LDL-Cholesterol Level	
Dietary Treatment	*Initiation Level, mmol/liter (mg/dl)*	*Minimal Goal, mmol/liter (mg/dl)*
Without CAD or 2 other risk factors	≥4.16 (160)	<4.16 (160)
With CAD or 2 other risk factors	≥3.38 (130)	<3.38 (130)
Drug Treatment		
Without CAD or 2 other risk factors	≥4.94 (190)	<4.16 (160)
With CAD or 2 other risk factors	≥4.16 (160)	<3.38 (130)

CAO=coronary artery disease, LDL=low-density lipoprotein

Dietary Treatment—Can It Be Done?

Only three dietary factors raise blood cholesterol levels: saturated fatty acids, dietary cholesterol, and excess calories resulting in obesity. The goal of the dietary treatment of hypercholesterolemia is to reduce the intake of these three dietary factors.

Unfortunately, dietary changes are difficult for many patients. Large clinical trials of dietary changes have generally resulted in relatively small average changes in dietary cholesterol, about 5% to 10%. Moreover, physicians commonly have little experience in promoting dietary changes, and most physicians' attempts at the dietary treatment of hypercholesterolemia are only cursory. With the appropriate guidance, however, many patients are able to change their diets substantially, obviating the need for drug treatment. Reductions in blood cholesterol levels of greater than 20% can, at times, be achieved.

Successful dietary change requires that patients be motivated to initiate new action and that they have information about the need to change their diets, specific skills to carry out new patterns of behavior, and a supportive environment in which to carry out change. Most physicians are comfortable with providing information to patients and providing support. More emphasis must be placed on assessing and enhancing motivation and on developing specific skills.

Motivation can be assessed by standard interviewing techniques, by assigning specific tasks such as a three-day diet record, and by scheduling a separate appointment to initiate diet therapy. Only motivated patients should be begun on intensive dietary therapy. Gentle attempts to enhance motivation by providing additional information, skills, and support should be continued, and such patients should be seen for regular follow-up visits to reassess motivation.

The development of specific skills for behavior change is more in the realm of behaviorists than of physicians; nonetheless, a number of simple skills can be taught by physicians to facilitate behavior change.[13] Specific goals can be negotiated between patient and physician. These should be tailored to the patient and should be measurable, achievable, recorded in the patient's record, and rewarded. Monitoring of behaviors, particularly food intake, allows patients to correlate specific behaviors with specific outcomes. Patients can

be taught to identify and avoid situations that impede the desired changes. Rehearsal or role-playing can be used to prepare for difficult unavoidable situations, and planning facilitates appropriate shopping and food preparation.

Making changes in small incremental steps allows the building of new experiences without taking excessive risks, and early successes are reinforced. Small failures are less damaging than large ones and can be used as effective teaching tools. Specific feedback by a review of diet records, the patient's report, and measured blood cholesterol levels provides the patient with support and further helps to build skills. Finally, patients can be taught that they are not expected to follow the diet 100% of the time. Even 90% compliance allows patients to have two meals per week with liberalized food choices without having a significant effect on their blood cholesterol levels.

Throughout this process the physician must maintain a positive attitude toward diet modification. Personal attempts by physicians at similar dietary changes will add considerable insight into this process.

Recommended Diets

The National Cholesterol Education Program recommends diet modification in two steps. The macronutrient composition of each is shown in Table 4.

The first goal of the diet is to reduce the total dietary fat to less than 30% of total calories. This has two purposes: to reduce the amount of saturated fat and to reduce the total calorie intake. The fat content of current US diets averages 35% to 40% of calories. Previous recommendations have been that patients who fail a step-one diet reduce their total fat consumption to less than 20% of their total calories. Recent evidence suggests that this is not necessary if saturated fat intake is further reduced.[14,15] Overweight patients, however, may need to reduce their total dietary fat to less than 20% to facilitate weight loss.

Reducing the intake of saturated fat is the single most important element of the dietary treatment of hypercholesterolemia. Current US diets contain an average of 13% to 17% of total calories as saturated fat. In the step-one diet, saturated fat should be decreased to less than 10%. This decrease in saturated fatty acid intake simultaneously results in the recommended decrease in total fat. A further reduction to less than 7% is recommended in the step-two diet. Saturated fats are primarily found in butterfat, beef and pork fat, and three plant oils—palm, palm kernel, and coconut—commonly used in commercial baked goods. More than 60% of the saturated fat in the US diet is contained in ten types of foods (Table 5).[16]

Results of a recent study suggest that the saturated fatty acids do not have equivalent effects on blood lipids.[17] Using liquid formula diets, Bonanome and Grundy compared diets with equal amounts of the saturated fatty acids palmitic (16:0) and stearic (18:0) and the monounsaturated fatty acid, oleic (18:1). Compared with the palmitic acid diet, the intake of both stearic and oleic acids resulted in a reduction in blood cholesterol values. Although stearic acid is an important fat in beef and chocolate, these foods also contain substantial amounts of palmitic acid and dietary cholesterol, and their intake should be restricted on a cholesterol-lowering diet. Polyunsaturated fats can be used to partially replace saturated fat in the diet. A one-for-one replacement of saturated fatty acids by polyunsaturated fatty acids results in a decrease in blood cholesterol levels. The current US intake is 7% of calories; the recommended intake is 10%. For patients attempting to lose weight, maintaining the 7% figure is preferable. Levels above 10% are no longer recommended owing to the lack of information concerning the long-term safety of such high intakes. Polyunsaturated fatty acids also lower HDL-cholesterol levels more than equal amounts of monounsaturated fatty acids.[18] Polyunsaturated fatty acids are found in several vegetable oils including safflower, sunflower, soybean, and corn.

Omega (ω)-3 fatty acids are also polyunsaturated fatty acids. These fatty acids have been shown to decrease blood triglyceride levels in high doses but have a variable effect on LDL- and HDL-cholesterol levels.[19,20] The major source of ω-3 fatty acids is fish oil. Consuming ω-3 fatty acids is not equivalent to consuming fish. Some fish, such as mackerel and salmon, contain relatively large amounts of ω-3 acids while others, such as swordfish, do not. Epidemiologic evidence suggests that eating fish, independent of the ω-3 fatty acid content, is associated with a decreased risk of coronary artery disease.[21] In any case, fish is an excellent dietary substitute for meat.

Until recently, monounsaturated fats were thought to have a neutral effect on blood cholesterol. Recent evidence suggests, however, that monounsaturated fatty acids are equivalent to polyunsaturated fats in lowering LDL-cholesterol levels when either is substituted for saturated fatty acids and do not show the HDL-cholesterol-lowering effect seen with polyunsaturated fatty acids.[18,22] The current US diet contains 14% to 16% of calories as monounsaturated fats,

TABLE 4.—*Macronutrient Composition of Step-One and Step-Two Diets*

Nutrient	Recommended Intake, % of Total Calories: Step-One Diet	Step-Two Diet
Total fat	<30	
Saturated fat	<10	<7
Polyunsaturated fat	Up to 10	
Monounsaturated fat	10-15	
Carbohydrates	50-60	
Protein	10-20	
Cholesterol	<300*	<200*
Total calories	To achieve desirable weight	

*Milligrams per day.

TABLE 5.—*Major Contributors of Saturated Fatty Acids in the American Diet**

Rank	Food	Dietary Saturated Fatty Acid, % of Calories
1	Hamburgers, cheeseburgers, meat loaf	9.3
2	Whole milk, whole milk beverages	9.1
3	Cheeses, excluding cottage cheese	7.3
4	Beef steaks, roasts	7.3
5	Hot dogs, ham, luncheon meats	7.0
6	Doughnuts, cookies, cake	4.8
7	Eggs	4.5
8	Pork, including chops, roasts	4.0
9	Butter	3.7
10	White bread, rolls, crackers	3.2
	Total	60.2

*From Block et al.[16]

mostly from animal fats. When the amount of dietary fat is decreased, a larger portion of monounsaturated fats will come from vegetable oils. Canola oil and olive oil are two vegetable oils that are high in monounsaturated fats and low in saturated fats.

Dietary cholesterol has a less important effect on blood cholesterol levels than dietary fat. Although increases in dietary cholesterol typically raise the blood cholesterol level, the increase is rarely striking and varies from person to person. An additional concern, however, is that dietary cholesterol is absorbed as chylomicrons that are degraded into cholesterol-rich chylomicron remnants, which themselves may be atherogenic. Dietary cholesterol is found in animal products including egg yolks, organ meats, some shellfish, butterfat, and animal flesh (including chicken and fish). Ten types of foods contribute more than 77% of the dietary cholesterol in the US diet (Table 6).[16] Interestingly, the list is similar to the saturated fat list.

In patients who are overweight, total calories should be reduced to attain a normal body weight. For many patients this is the most difficult part of a cholesterol-lowering diet. Calorie reduction and weight loss will often, but not always, decrease LDL-cholesterol levels. Blood triglyceride levels, however, virtually always decrease, and HDL-cholesterol levels commonly rise.

Changes in dietary fiber intake can also result in cholesterol lowering. Dietary fiber is either insoluble or soluble. Insoluble fiber adds bulk to the stool but has no significant effect on blood cholesterol levels. High intakes of soluble fiber—15 to 25 grams a day—however, have been shown to decrease blood cholesterol levels by 10% to 20%.[23,24] Soluble fibers include pectins, certain gums, and psyllium. A common source of one of the cholesterol-lowering gums, β-glucan, is found in oats and beans.

Alcohol has no direct effect on LDL-cholesterol levels but does increase both triglyceride and HDL-cholesterol levels.[25] It is not clear if the associated rise in HDL-cholesterol offers protection against coronary artery disease. Patients who consume moderate amounts of alcohol—less than 2 ounces a day—can continue to do so; patients who do not drink should not be encouraged to do so.

Aerobic exercise facilitates weight loss and has a direct effect on serum lipids, lowering LDL-cholesterol and triglyceride values, and increasing HDL-cholesterol levels. Recent evidence suggests that a well-designed exercise program is as effective as diet in improving the blood lipid profile.[26] Patients should be encouraged to exercise aerobically for 20 to 30 minutes four to five times per week. A heart rate of 70% to 80% of maximum predicted heart rate should be achieved and sustained during exercise.

TABLE 6.—*Major Contributors of Dietary Cholesterol in the American Diet**

Rank	Food	Dietary Cholesterol, %	mg/d
1	Egg yolks	35.9	162
2	Beef steaks, roasts	8.7	39
3	Hamburgers, cheeseburgers, meat loaf	7.3	33
4	Whole milk, whole milk beverages	5.4	24
5	Hot dogs, ham, luncheon meats	4.3	20
6	Pork, including chops, roasts	3.6	16
7	Doughnuts, cookies, cake	3.6	16
8	Cheeses, excluding cottage cheese	3.1	14
9	Liver	2.7	12
10	Chicken and turkey, excluding fried	2.6	12
	Total	77.2	348

*From Block et al.[16]

Practical Aspects in Designing Diets

In practical terms, most patients and physicians are unable to differentiate between the step-one and step-two diets. An alternative is to begin with a qualitative approach, followed by a quantitative approach.

The qualitative approach divides foods into those that should be chosen and those that should be decreased. A wide variety of excellent patient education materials are available to facilitate this process. Food lists can then be tailored to patients' individual eating habits and food preferences. This approach should be followed for at least three months with visits and blood cholesterol determinations one and three months after the diet's initiation.

Further reducing the saturated fat intake to less than 7% of total calories and dietary cholesterol to 200 mg per day requires a more quantitative approach.[27] By estimating patients' daily energy requirements and calculating the daily intake of saturated fat, highly motivated patients can be instructed to keep daily food records tracking their saturated fat intake. Although a number of patient-oriented books and manuals are available to assist patients with this process, a referral to a registered dietician is often necessary to adequately teach the step-two diet. As with the step-one diet, patients should be seen one and three months after initiation.

Drug Therapy—Have the Magic Bullets Arrived?

Patients with elevated LDL-cholesterol levels for whom six months of intensive dietary therapy fails should be considered for drug treatment. The decision to initiate drug therapy must be made after careful deliberation and discussion with the patient. Throughout the process of managing hypercholesterolemia, but particularly when initiating drug therapy, the physician and the patient should realize that they are treating a risk factor, not a disease. Although many patients will choose to do everything possible to decrease their risk of coronary artery disease, other patients may prefer to take the risk and avoid drug therapy.

The principles of successful drug treatment of hypercholesterolemia are analogous to drug treatment of hypertension. Patients should be clear about the goals of therapy and the need for long-term treatment. Careful attention must be paid to common side effects and their prevention. Every drug, but particularly the bile acid-binding resins and nicotinic acid, should be begun at low dosages. Once- or twice-a-day dosing is preferred whenever possible. Frequent follow-up and monitoring are necessary to prevent complications and maximize compliance. The need for concurrent diet therapy should be emphasized. Periodic trials of decreasing drug doses or discontinuing the use of the medications in well-controlled patients should be considered.

The major drugs for consideration by primary care providers are the bile acid-binding resins, cholestyramine resin and colestipol; the B-complex vitamin, nicotinic acid; the fibric acid derivative, gemfibrizol; and the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, lovastatin. A number of other agents are under active investigation, particularly other fibric acid derivatives and HMG-CoA reductase inhibitors, and may soon be available.

TABLE 7.—*Lipid-Modifying Effects of Major Cholesterol-Lowering Medications*

Drug	Lipids, % Δ		
	LDL-Cholesterol	HDL-Cholesterol	Triglycerides
Nicotinic acid	−15-20	+30-35	−25-30
Resins	−15-25	+5	+10
Gemfibrizol	−15	+15-20	−35-50
Lovastatin	−20-45	+10	−20

HDL=high-density lipoprotein, LDL=low-density lipoprotein

In selecting drugs from the current list of available drugs, at least five factors should be considered. These are their lipid-modifying effects, proven efficacy, long-term safety, convenience and side effects, and cost. Each of the four classes of medications have advantages and disadvantages in these regards. The choice of one drug over another will reflect both physician biases about drug use and patient preferences. Although the lipid-modifying effects of each of the drugs are excellent, they are not all equivalent (Table 7). Nicotinic acid, the bile acid-binding resins, and gemfibrizol have approximately equivalent LDL-cholesterol-lowering effects while lovastatin is about twice as effective. Changes in HDL-cholesterol levels are more diverse. The use of nicotinic acid and gemfibrizol results in excellent increases in HDL-cholesterol, lovastatin has an intermediate effect, and the resins a modest effect. Changes in triglyceride levels are even more varied. Nicotinic acid, gemfibrizol, and lovastatin all have significant triglyceride-lowering effects, whereas the resins elevate triglyceride levels. Although changes in triglyceride levels appear to have little effect on coronary artery disease, the triglyceride-raising effect of the resins may be important in patients with pronounced hypertriglyceridemia (>54.5 mmol per liter [500 mg per dl]) due to the risk of provoking pancreatitis.

The long-term efficacy and safety of these drugs has been investigated in the large clinical trials discussed earlier. Only nicotinic acid has to date been shown to reduce total mortality. Nicotinic acid, cholestyramine, and gemfibrizol reduce coronary disease end points. All three drugs have been shown to be safe in trials of five to seven years. Although lovastatin has not yet been studied in a large clinical trial, most authorities are confident that its use will be extremely effective in reducing the incidence of coronary artery disease. The unresolved concern is, of course, its long-term safety. Only about 1,000 patients have been carefully observed for at least a year while taking lovastatin. A quarter of these have been observed for up to four years. These are insufficient numbers to detect a relatively rare but life-threatening complication of the drug. Since its public release, however, hundreds of thousands of patients have been treated with lovastatin. Any serious side effects should be seen in the near future. My practice is to reserve lovastatin therapy for patients with genetic hyperlipoproteinemia and substantially elevated blood cholesterol levels, refractory patients, and patients in whom compliance and convenience are paramount.

Differences in medication cost are also noteworthy. Surprisingly, there are minimal differences in the wholesale cost among these drugs when equipotent doses are compared.[28] The only major exception is generic nicotinic acid, which is approximately a sixth the cost of the other medications.

In practical terms, differences in side effects and convenience and their influence on compliance often determine the choice of medication in a given patient. Although nicotinic acid offers a number of advantages as noted above, it can be a difficult drug to use for many patients. The major obstacle to its use is the severe flushing experienced by most patients. The flushing is prostaglandin mediated and can often be inhibited by taking one aspirin 30 minutes before each dose of niacin. Sustained-action nicotinic acid preparations are nearly as effective at modifying lipids, usually cause less flushing, but are more expensive. Other common side effects of nicotinic acid include gastrointestinal distress, hepatic toxicity, glucose intolerance, hyperuricemia, and dry eyes. Nicotinic acid should be used with caution in patients with diabetes mellitus, and its use should be avoided in patients with active gout, liver disease, or peptic ulcer disease.

To minimize side effects and maximize long-term patient acceptance, nicotinic acid therapy should be begun at low doses—usually 100 mg with the evening meal. The dosage can be increased every four to seven days until a dosage of 1.5 to 2.0 grams per day is reached. If the goal LDL-cholesterol level has not been reached, the dosage can be increased to 3 to 6 grams in two or three doses per day.

The most frequent side effects of the bile acid-binding resins cholestyramine and colestipol are gastrointestinal. Constipation, abdominal pain, heartburn, nausea, belching, and bloating are common, and patients often complain of the medications' gritty taste and a dry mouth. Side effects may be avoided by taking the resins with fruit juice instead of water, increasing the intake of fluid and dietary fiber to prevent constipation, and taking them with meals. Stool softeners may occasionally be useful. A recently marketed confectionery form of cholestyramine may be preferable for some patients, but it is expensive and high in calories. Resins may also interfere with the absorption of many other drugs. Other medications should be taken an hour before or four hours after the resins.

As with nicotinic acid, resin therapy should be begun at doses well below the anticipated maintenance dose. A dosage of 5 grams of colestipol or 4 grams of cholestyramine is begun once a day, increasing slowly to 20 to 30 grams of colestipol or 16 to 24 grams of cholestyramine per day in split doses.

Gemfibrizol is the easiest to use of the first-line medications, and it is usually well tolerated. The most common side effects are upper gastrointestinal symptoms. Abnormalities of hematologic variables and liver enzyme levels and myositis have infrequently been reported. The dosage is usually begun at 300 mg per day with the evening meal—most cholesterol is made at night—and advanced to 600 mg twice a day.

Lovastatin is also easy to use and well tolerated. Although side effects are infrequent, concerns about its long-term safety persist. Liver enzyme abnormalities and myositis with creatine kinase elevations require discontinuing the therapy in 1% to 2% of patients and should be monitored during therapy. Severe myositis and associated renal failure have been reported, usually when lovastatin has been used with other medications such as cyclosporine or gemfibrizol. Initial concerns about an increased incidence of lens opacities with the use of lovastatin have not been substantiated. The dosage of lovastatin is begun at 20 mg with the evening meal and can be increased up to 80 mg per day in split doses.

In patients in whom a single cholesterol-lowering medi-

cation has been insufficient, combinations of two or three of these medications can be used. The combined use of gemfibrizol and lovastatin, because of the greater incidence of severe myositis, should be reserved for particularly difficult patients. As with antihypertensive medications, lower doses of two agents may be preferable in preventing side effects than large doses of a single agent.

Summary

We now have sufficient evidence to recommend an aggressive program of the detection and treatment of hypercholesterolemia. All adult patients should be screened and evaluated, and treatment decisions should be based on their LDL-cholesterol levels and the presence or absence of other risk factors. Diet therapy should be initiated in motivated patients for three to six months progressing from a qualitative to a quantitative approach. Patients with persistent elevations in their LDL-cholesterol levels who accept drug therapy can be begun on a regimen of nicotinic acid, gemfibrizol or bile acid-binding resins, and, when necessary, lovastatin.

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Epitomes
Important Advances in Clinical Medicine

Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Botulinum Toxin Therapy for Torticollis

BOTULINUM TOXIN has been used for some years to treat ophthalmologic conditions such as strabismus and blepharospasm in which there is inappropriate or unbalanced muscle activity. The toxin binds rapidly and with high affinity to nerve terminals, so that small amounts injected locally into overactive muscles produce focal weakness without causing any serious systemic side effects.

Recent studies have focused on the role of botulinum toxin in the treatment of spasmodic torticollis and other dystonic disorders. In torticollis, which is usually idiopathic and attributed to basal ganglia dysfunction, there is an abnormal posture of the head due to the overactivity of certain neck muscles. Most of the drugs that have been used in its treatment are of limited usefulness, producing either little or no benefit or mild benefit at the expense of side effects that are often distressing. Accordingly, there have now been several trials of using botulinum toxin to treat torticollis. In general, these studies have shown that compared with placebo, botulinum toxin administered to overactive cervical muscles can produce subjective improvement in between 50% and 80% of patients. The benefit may involve both a reduction in abnormal movements or postures and a reduction in pain. Objective benefit may also occur but is more difficult to show, probably because of the insensitivity of the objective rating scales that are available. The benefit may last for several months but eventually wanes unless the muscles are reinjected with the toxin.

Overactive muscles can be injected either in the motor end-plate region or at sites distributed throughout the length of the muscle, with similar results. Various doses have been used in the different published studies but usually are less than a total of 300 units at any one time or 180 units to any single muscle. The estimated median lethal dose for humans is 2,500 to 5,000 units.

Side effects are typically minor and short-lived and include local pain or discomfort about the site of injection, neck weakness, malaise, and occasionally dysphagia (which may last for a few days). The cause of the dysphagia is not clear but may relate to a local spread of the toxin to the muscles of deglutition. There is neurophysiologic evidence that local injections of botulinum toxin produce subtle effects on neuromuscular transmission at distant sites, but these effects are not detectable clinically with the usual doses administered for torticollis.

In some patients, botulinum toxin injections are only briefly effective despite a persistent relaxation of previously overactive muscles, suggesting that the pattern of muscle activity in torticollis may change after botulinum toxin injections, just as it may change following surgical procedures such as rhizotomy, peripheral nerve section, or muscle section. Botulinum toxin therapy for torticollis is now being used at several major medical centers, but the toxin is not yet approved by the Food and Drug Administration for general use.

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Treating Febrile Seizures

FEBRILE SEIZURES, which occur in about 3% of children between the ages of 3 months and 5 years, often recur (30% to 40%) but are rarely associated with long-term neurologic sequelae or the development of epilepsy or nonfebrile seizures (7% by age 25). The development of nonfebrile seizures later in life occurs more frequently in infants whose febrile seizures are "complex"—that is, focal, prolonged over 30 minutes, or repeated seizures with the same illness—and particularly if these complex features appear in an infant who is already known or thought to have neurological abnormalities. The risk of nonfebrile seizures appearing up to the age of 25 years ranges from 2.4% among children with simple febrile seizures to 49% in the small number having all three complex features.

In a discussion of the treatment of febrile seizures, attention must first be directed to the acute event. Most (95%) febrile seizures are short-lived (less than 30 minutes); 81% are nonrecurrent during a particular febrile illness. Anticon-

vulsant therapy is indicated if the seizures have not stopped before the infant reaches a physician's office or emergency department. Parenteral lorazepam, 0.05 to 0.1 mg per kg body weight, is the antiepileptic drug now preferred by many pediatric neurologists, though the use of parenteral phenobarbital, 10 mg per kg, is still popular. If the seizure is short, then refraining from treating with antiepileptic drugs is acceptable therapy. The infant should then be evaluated for the source of the fever, and the appropriate antipyretic therapy started. The place of routine lumbar puncture in evaluating febrile seizures is debated, but most physicians agree that infants with focal or unilateral seizures, suspicious findings on the physical examination, such as rash or petechiae, hypotension, or grunting respirations, or on a neurologic examination, such as neck stiffness, abnormal tone, an altered level of consciousness, eye deviation, or abnormal fontanel tension, should be tapped. If it is likely that the parents will not comply with follow-up in the next few days, then a lumbar puncture should be considered.

The issue of long-term therapy must be considered in light of the fact that the prophylactic use of antiepileptic drugs, either short- or long-term, will reduce the incidence of recurrent seizures but have no effect on the risk of the later development of nonfebrile seizures. There is also no compelling evidence that febrile seizures per se cause neurologic injury, though some clinicians think that severe or recurrent febrile seizures occur more frequently in children in whom temporal lobe epilepsy ultimately develops. Some physicians advocate instituting the prophylactic use of antiepileptic drugs in so-called high-risk infants, that is, those younger than 12 months, or who have had a previous complex febrile seizure, and those infants with developmental delay, evidence of a neurologic impairment before the seizure, or with temporary neurologic abnormalities after a seizure (Todd's paralysis). None of these factors, however, except for the age at the initial seizure, are major predictors of recurrence. For example, most complex seizures occur as the first seizure and are not predictive of subsequent seizures. These facts certainly support a nontreatment approach to all children with febrile seizures.

Continuous prophylactic therapy has traditionally been accomplished with phenobarbital, though using valproic acid and primidone has also been effective. All of these drugs have substantial and on rare occasions lethal side effects, which has led to the use of intermittent prophylaxis with rectal diazepam. The parenteral solution can be instilled in the rectum at a dose of 0.5 mg per kg (maximum dose 10 mg) at the first sign of a fever or when a seizure occurs. The former approach has been shown by many investigators in Europe and in yet-unpublished studies in this country to reduce the risk of recurring febrile seizures. Administering the drug when the seizure begins, which is now being done with severely epileptic children, reduces the duration of the recurrent seizure and obviates a trip to an emergency department. Side effects are few. The rectal use of lorazepam has also been effective in aborting status epilepticus in epileptic infants and children and will probably become the drug treatment of choice in the intermittent prophylaxis of febrile seizures.

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Optimal Drug Management of Parkinson's Disease

FOR SEVERAL YEARS A COMBINATION PRODUCT OF CARBIDOPA AND LEVODOPA (Sinemet) has been the principal drug in the treatment of Parkinson's disease. We favor beginning a careful titration of the drug within the first year or two of clearly defined symptoms, at the point when a patient begins to be disabled. This strategem is based on evidence showing that early treatment results in a longer lifespan and that late complications have been related to the progression of the disease and not to the duration of dopa treatment. An opposing claim is that dopa has a finite usefulness and treatment is better postponed until later in the course of the disease.

Sinemet 25-100 (containing 25 mg of carbidopa and 100 mg of levodopa) is typically administered with half a tablet two or three times a day with food, gradually increasing over the next few months to three or four whole tablets a day. If adequate benefits are not achieved by then, switching to Sinemet 25-250 (carbidopa, 25 mg, and levodopa, 250 mg) may be helpful, using half tablets initially and whole tablets subsequently. Each stepwise increase should be given only after a careful evaluation of rigidity, akinesia, tremor, activities of daily living, and possible side effects, particularly dyskinesia and confusion. Patients should be seen every three to four months.

As the duration of disease increases, the efficacy of each dosage may gradually decrease from four or five hours to one or two hours. This "wearing off" can be treated by administering small doses of carbidopa-levodopa at three-, two-, or one-hour intervals during the day and one or more doses at night. The total daily dose should remain constant.

After some years, choreoathetoid dyskinesia may alternate with the wearing-off effect, resulting in a state that fluctuates between reasonably good control, involuntary movements from too much dopa, and parkinsonian akinesia and tremor. This, too, may be treated by shortening the interval between doses or by adding the dopamine agonist, bromocriptine mesylate (Parlodel). The dosage of bromocriptine, 2.5 mg, is begun with a half or a quarter tablet once or twice a day, gradually increasing to 15 to 25 mg a day over several months.

Another approach is to begin therapy in a previously untreated patient with bromocriptine or pergolide mesylate, a new dopamine agonist soon to be available. Eventually, carbidopa-levodopa needs to be added to this regimen, but some neurologists feel that some of the late side effects of dopa may be lessened or postponed by giving dopa-agonist therapy first. A variation on this is to begin therapy with levodopa combined with a dopamine agonist. Rinne, using a mean daily dose of dopa (combined with a dopa-decarboxylase inhibitor) of about 500 mg, plus a mean dose of bromocriptine, 22 mg, found less end-of-dose disturbance and peak-dose dyskinesia at the end of five years than with the use of levodopa alone. It is critical not to begin giving both drugs at the same time. To separate the immediate beneficial and the side effects of the two drugs, we recommend starting with one drug, gradually increasing to the desired dosage, and then doing the same with the second drug.

Other drugs acting synergistically with dopa include anticholinergics such as trihexyphenidyl hydrochloride and benztropine mesylate. Amantadine hydrochloride may have both short- and long-term benefits, particularly for tremor.

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Electrodiagnosis of Neuromuscular Disorders

ELECTRODIAGNOSTIC TECHNIQUES can be of help in the diagnosis, management, and prognosis of neuromuscular syndromes. Motor nerve conduction is determined by recording the compound muscle action potential, usually from a small intrinsic hand or foot muscle, while the nerve is stimulated at two locations. The distal latency reading is subtracted from the proximal latency reading and the difference divided into the distance measurement. Abnormal latencies and waveforms may indicate axonal loss or the presence of nerve conduction block resulting from demyelination and assist in locating the site of such abnormalities.

The F wave, resulting from electrical stimulation of the motor nerve, is an example of a "late response." It occurs when an antidromically conducted action potential reaches the motoneuron and is fired back out to the periphery. Prolonged latencies of late responses when nerve conduction is normal indicate the presence of proximal neuropathy, usually demyelination (acute Guillain-Barré syndrome). The F wave is conducted over the ventral root and is not a reflex. In some muscles, such as the soleus or flexor carpi radialis, it is possible to record the H reflex, which results from the activation of muscle spindle afferents. The H reflex uses the spinal monosynaptic reflex requiring the dorsal root. Disorders selectively involving the dorsal root can be detected by comparing the F-wave and H-reflex responses.

Sensory nerve action potentials are recorded from the skin or by near-nerve needle recording. Cerebral and spinal evoked potentials can also be recorded after nerve stimulation. These potentials often require signal averaging to record. The technique permits an investigation of disorders of the sensory nerve affecting large myelinated fibers and connections to cerebral cortex.

A repetitive stimulation of motor nerves while recording the compound muscle action potential (CMAP) is used to evaluate neuromuscular transmission. A decline in the amplitude of the CMAP at slow rates of stimulation indicates a postsynaptic defect; the reduced amount of acetylcholine produced following each nerve impulse finally falls below the level sufficient to activate some muscle fibers. A presynaptic defect, as seen in botulism or the Lambert-Eaton syndrome, causes an increase in amplitude with high rates of stimulation (>10 Hz) as the release of acetylcholine is facilitated by increased levels of extracellular calcium associated with repetitive stimulation. The amplitude of the CMAP from a condition of rest is below normal.

A quantitative analysis of the amplitude, duration, and waveform of the motor unit action potential recorded by a needle electrode can be used to detect signs of motor unit loss, denervation, reinnervation—early and late—and muscle fiber loss. This technique can characterize the extent and severity of neurogenic atrophy as well as of myopathy.

The single-fiber electrode records the potentials of single muscle fibers from within a small electrode recording area. Two or more muscle fiber potentials can be recorded from within the same motor unit. By triggering the sweep of an oscilloscope with the single-fiber potential and delaying the display of action potentials, the synchrony of the firing of fibers and their density within the motor unit can be determined. Such studies are helpful in diagnosing disorders of the neuromuscular junction when the results of other studies are normal.

The latency and amplitude of reflexes can be used to assess central connections important for the reflex and the integrity of each limb. For example, the blink reflex can be used to evaluate an oligosynaptic ipsilateral response of orbicularis oculi muscle in response to stimulation of the trigeminal nerve, as well as a polysynaptic, bilaterally represented later response with pathways in the pons and medulla. Combined with motor conduction studies of the seventh nerve, lesions within the pons can be differentiated from those affecting one limb of the reflex.

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Nervous System Effects of Toluene and Other Organic Solvents

ORGANIC SOLVENTS are industrial compounds that produce neurologic syndromes related to both acute and chronic intoxication. Because hundreds of new organic compounds are introduced each year, many previously unsuspected toxic effects have been recognized. Solvents are highly lipophilic, which explains their distribution to organs rich in lipids, such as the brain. Although extremely high concentrations of all volatile organic solvents produce nonspecific effects, such as encephalopathy, many of these solvents produce relatively specific neurologic syndromes with lower level, longer term exposure. Long-term or persistent specific effects on the nervous system vary with the duration of exposure and whether the central nervous system (CNS) or the peripheral nervous system is primarily affected.

Long-term exposure to the aliphatic hydrocarbons, such as *n*-hexane and methyl butyl ketone, is typically associated with the development of peripheral neuropathy. Animal models developed using these compounds are classic examples of target-organ toxicity affecting the peripheral nervous system. The aromatic hydrocarbons, such as toluene, have been known to cause both acute and chronic CNS toxicity in humans for more than two decades, but because of the lack of an animal model of neurotoxicity and the small number of human cases, understanding the pathogenesis of the CNS effects of toluene has only come recently.

Toluene is the most widely used of the organic solvents

and is a major component in many paints, lacquers, glues and adhesives, inks, and cleaning liquids. As with other solvents, inhalation is the major route of entry, though some absorption occurs percutaneously. Of all the solvents, toluene seems to have the highest potential for abuse, and recent studies of habitual inhalant abusers of toluene-containing products have begun to shed light on its chronic CNS effects.

Acute intoxication with toluene produces euphoria, giddiness, and a cerebellar ataxia. Higher levels of exposure will lead to progressively greater degrees of a nonspecific encephalopathy. With long-term abuse (usually ten years or more of daily use), neurologic impairment will develop in almost two thirds of abusers. Neurologic abnormalities vary from mild cognitive impairment to severe dementia, typically associated with other neurologic signs such as cerebellar ataxia, corticospinal tract dysfunction, oculomotor abnormalities, tremor, deafness, and hyposmia. Cognitive dysfunction is the most disabling and frequent feature of chronic toluene toxicity and may be the earliest sign of permanent CNS injury. A recent magnetic resonance imaging and neuropathologic study of long-term toluene abusers has shown evidence of diffuse CNS white matter changes, suggesting that the primary effect of toluene may be on CNS myelin or myelin-producing cells.

While it is now clear that habitual toluene abuse leads to permanent multifocal CNS injury from effects on white matter, it is less obvious what happens in industry, where workers have exposure to much lower, presumably "safe," levels of toluene and other solvents. Exposure to solvents in the workplace is a particularly common situation. Unlike exposure in cases of abuse, where dramatic clinical neurotoxicity is seen following high-level acute and chronic exposures, studies over the past two decades, primarily from Scandinavia, report a syndrome that develops after low-level chronic exposure. This syndrome has been called the "psycho-organic syndrome" primarily because of the nonspecific nature of the signs and symptoms. The most common symptoms of the syndrome are poor memory, headache, fatigue, concentration difficulties, and personality changes (irritability, depression, emotional lability). The results of the neurologic examination in these persons, as well as neuroimaging and neurophysiologic studies, are normal. Only extensive neuropsychological testing has suggested cognitive dysfunction. Athough these initial studies were uncontrolled, nonrandomized, and unblind, the psycho-organic syndrome was widely accepted as a clinical illness and soon became a major problem for industry, the legal profession, and physicians. Recent studies, however, have cast doubt as to whether or not the syndrome exists. Several recent, well-designed studies, including one by the Danish group that first reported this condition, have shown no neuropsychological differences between workers with or without exposure to solvents.

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Peripheral Neuropathy Associated With Human Immunodeficiency Virus Infection

PERIPHERAL NEUROPATHIES occur in a third or more of patients with human immunodeficiency virus (HIV) infection, with the most common type being distal axonal polyneuropathy in patients with the acquired immunodeficiency syndrome (AIDS). Three other types of peripheral neuropathy are also widely recognized: inflammatory demyelinating polyneuropathy, mononeuropathy multiplex, and progressive lumbosacral polyradiculopathy.

In patients with distal axonal polyneuropathy, sensory symptoms typically develop in the feet as the initial complaint. While a third of patients with AIDS have mild distal numbness or paresthesias, 10% of patients with constitutional symptoms from HIV infection—more often AIDS than AIDS-related complex—present for a neurologic evaluation of painful feet. Depressed or absent tendon reflexes only at the ankle and a decreased perception of sensation in the feet are the predominant abnormalities detected on examination. Although rarely a complaint, mild distal weakness may be present. Nerve conduction studies show decreased amplitude of sensory nerve action potentials as the predominant abnormality, but mild slowing of sensory and motor conduction velocity may also be found. Although patients treated with azidothymidine and other patients without treatment have rarely improved, the condition of most patients continues to worsen despite treatment with azidothymidine, prednisone, or plasmapheresis. Treatment is symptomatic, with the use of tricyclic antidepressants often reducing the severity of pain. The pathogenesis of this neuropathy is unknown, with possible causes including nutritional deficiency, drug toxicity, and infection.

Patients with inflammatory demyelinating polyneuropathy have weakness either acutely—with the clinical features of the Guillain-Barré syndrome—or chronically. In addition to weakness that includes proximal muscles, tendon reflexes are absent. Sensory symptoms and signs are minor. Electrodiagnostic studies provide evidence for an acquired demyelinating polyneuropathy, with severely reduced conduction velocities, multifocal conduction block, or both. Either of these polyneuropathies may be the initial symptom of a patient with undiagnosed HIV infection, so cerebrospinal fluid (CSF) pleocytosis in a patient with inflammatory demyelinating polyneuropathy suggests the need to determine the HIV antibody status. Nerve biopsy specimens reveal segmental demyelination and mononuclear cell infiltration, and an autoimmune pathogenesis is generally accepted. These polyneuropathies usually respond well to treatment with plasmapheresis, either alone in the acute form or possibly together with the use of prednisone in the chronic form.

Patients with mononeuropathy multiplex and HIV infection typically present with multifocal sensory loss that is more prominent than weakness. Cranial nerves, particularly the trigeminal and facial, may be involved. Patients with this neuropathy typically have constitutional symptoms and other features of AIDS-related complex. Electrodiagnostic studies usually provide evidence for axonal degeneration that varies in severity in different nerve distributions. Nerve biopsy specimens contain perivascular and endoneurial inflammatory cell infiltrates and confirm axonal degeneration; an autoimmune pathogenesis is generally accepted. The neuropathy spontaneously remits in half of patients. Some with progres-

sion respond to plasmapheresis or prednisone therapy, with or without the additional features of a chronic inflammatory demyelinating polyneuropathy developing. The remaining patients with progression go on to have more confluent distal symptoms and signs typical of distal axonal polyneuropathy and do not respond to immunotherapies.

Progressive lumbosacral polyradiculopathy occurs predominantly in patients with AIDS. Progressive weakness, numbness, and pain of the legs develop subacutely along with impaired sphincter control. A CSF examination is the most important diagnostic test. In polyradiculopathy due to cytomegalovirus (CMV) infection, the CSF typically has a polymorphonuclear pleocytosis (0.5×10^6 per liter or greater), a low glucose level, and an elevated protein content. Ascending paralysis typically leads to death within two months, but early treatment of CMV polyradiculopathy with ganciclovir has been effective in at least some cases. In one patient with a positive CSF VDRL, antibiotic therapy was curative for a syphilitic polyradiculopathy. Other patients have presented with similar neurologic symptoms and signs but with a CSF that had fewer cells and from which CMV could not be cultured. Some of these patients have had lymphomatous cells on CSF cytologic examination, and these patients have died. Others with normal cytologic findings have shown either continued progression or spontaneous remission; the cause in these cases is unknown.

Thus, peripheral neuropathies are common in association with HIV infection, and each type suggests a particular diagnostic and treatment strategy.

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Diagnosing Heavy Metal Intoxication in Patients With Neurologic Signs

NERVOUS SYSTEM SIGNS are common in acute and chronic cases of heavy metal poisoning. These include peripheral neuropathy from lead, arsenic, organic and inorganic mercury, and thallium; mental retardation or dementia from organic and inorganic mercury and lead; psychosis from arsenic and inorganic mercury; encephalopathy with seizures from lead and arsenic; and visual disturbances or ataxia from organic mercury.

Most toxicology laboratories use atomic absorption spectroscopy to analyze specimens for heavy metals. This method can detect common heavy metals, is accurate and quantitative, and can be done on blood, urine, hair, or other tissues. The toxicology laboratory should be informed which heavy metals are suspected because the instrument must be adjusted for each element analyzed. The choice of specimens to submit depends on how recent the exposure was and the duration of the intoxication. In general, blood is the most useful specimen in acute intoxications (within three days), except for arsenic (where, because of arsenic's short half-life, urine is also helpful). For chronic intoxications (weeks to months), urine or hair provides the most useful information.

Care should be taken in collecting specimens to avoid environmental contamination. Whole blood is preferred over serum for heavy metal analysis because metals often accumulate within erythrocytes. The blood specimen should be collected in a heparinized, trace metal-free glass tube. A 24-hour urine specimen should be collected in an acid-washed container (the inside of a plastic or glass container is washed with a solution of 0.1 molar hydrochloric acid, rinsed with distilled water, and then dried). Hair can be used to detect chronic metal intoxications from arsenic and mercury. For the specimen, 50 to 100 strands of scalp hair are cut close to the scalp. The strands are oriented so that the bases of the hairs are together. The bundle of hair should then be cut into thirds and each group of hair strands separately placed into trace metal-free glass tubes that are labeled proximal, middle, or distal scalp hair. A metal measurement of all three specimens will provide an estimation of the duration of the exposure because hair grows about 1 cm per month. Differences in metal content in the three hair sections also decrease the likelihood that the metal accumulation occurred from external environmental contamination, such as from hair washing.

In interpreting heavy metal analyses, it is important to know the normal values from a particular toxicology laboratory. In general, levels that are consistent with significant heavy metal intoxication are at least twofold to threefold above the normal levels for a laboratory. If borderline levels of lead or another heavy metal occur in a patient thought to have chronic intoxication, a diagnostic challenge with calcium disodium ethylenediaminetetraacetate (EDTA) may be considered. In this situation, a baseline 24-hour urine specimen is collected. A second 24-hour urine collection is started and the adult patient is given EDTA, 1 gram in 250 ml of 5% glucose solution given intravenously over one hour. The EDTA dose is repeated 12 hours later. A pronounced increase in the heavy metal content in the second urine collection, usually threefold to fivefold over the baseline specimen, implies substantial exposure to the heavy metal with increased body burden.

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New Strategies in Stroke Treatment

THE INCIDENCE OF STROKE has decreased significantly in recent decades, due largely to a better management of risk factors such as hypertension. This improvement has not been matched by the results of treating acute stroke, which has been directed at restoring or amplifying altered perfusion and preventing the aggregation of formed elements of blood. Using aspirin reduces the incidence of stroke after a transient ischemic attack, ticlopidine hydrochloride use is under study, and other antiplatelet drugs have not been shown to be effective. Heparin and sodium warfarin administration reduces the incidence of cardiogenic emboli but is not beneficial in

other types of stroke. The use of anticoagulants in progressing stroke, while customary, has unproven benefits. Thrombolytic agents carry a significant risk of hemorrhage. Dextran sulfate, hemodilution, and pentoxifylline are ineffective.

Our understanding of the pathophysiology of acute cerebral ischemia has attained new levels in recent years. Attention was focused initially on energy substrate availability for ischemic neurons, but high intracellular glucose may increase intracellular acidosis. Other potentially cytotoxic events include alterations of the homeostasis of intracellular ions (especially calcium), an imbalance between prostacyclin and thromboxane production, a net increase in free radical species, and changes in the blood-brain barrier with the formation of edema and subsequent further impairment of the diffusion of oxygen and glucose into the neuron. Each of these has led to the development of a new therapeutic strategy, the results of which are summarized.

The most exciting development in the treatment of cerebral ischemia is recognizing that excitatory and other neuropeptides are released after ischemia and may potentiate cellular damage by augmenting calcium flux into neurons, resulting in their untimely demise.

The mechanisms of the neurotoxicity of calcium influx in ischemia, recently reviewed, are complex. Although calcium channel blockers also affect the vascular tone, recent work indicates that their effect on the calcium homeostasis of the neuron may play a more central role in ischemic damage than previously appreciated. Studies in animals, using centrally acting calcium channel blocking agents such as nimodipine and lidoflazine, have persuasively shown a consistent and substantial beneficial effect on ischemic brain. Furthermore, a single-blind study of the effect of nimodipine use on the clinical course of patients with acute ischemic stroke showed significant functional improvement in the treated group. An additional double-blind study has also shown the use of nimodipine to significantly reduce morbidity and mortality. Currently, multicenter double-blind trials are being carried out to further study the effects of these calcium channel blocking agents in acute cerebral ischemia.

Yet another means of approaching calcium neurotoxicity involves the neurotransmitter mediation of neuronal calcium channels. Glutamate is a known excitatory transmitter found in large concentrations in human cortex and hippocampus. Studies completed in the past 15 years have shown that glutamate is a powerful neurotoxin and that its blockage or antagonism greatly diminishes the sensitivity of central neurons to ischemia. The *N*-methyl-D-aspartate (NMDA) subclass of glutamate receptors has the unique characteristic of being linked to calcium-permeable channels. Studies in animals using both a nonspecific excitatory amino acid-receptor antagonist and specific NMDA-receptor antagonists have shown a decrease in stroke size, deficits, and the percentage of severely ischemic neurons. As yet, there is nothing approved for clinical use.

While experimental data have convincingly shown that administering glucose before cerebral ischemia in animals seriously worsens the postischemic outcome, the interpretation of clinical studies in humans is open to debate. One problem is that the critical variable—intracellular glucose—cannot be measured. Nevertheless, it would seem prudent to minimize administering glucose until more definitive data are available.

Several studies indicate that the main cause of early death in patients with stroke is swelling of the ischemic hemisphere and the resulting transtentorial herniation. The results of clinical trials that have investigated the effect of glycerol or dextran use in acute stroke have been inconsistent. Some studies have shown benefits, some have not.

Additional approaches to metabolic treatment involve prostaglandin biosynthesis. There are several metabolic intermediaries in the synthetic pathway that are potentially harmful to intact neurons. These include active oxygen species (free radicals), thromboxane, and leukotrienes. During incomplete ischemia it is postulated that the normal biosynthetic pathway is altered such that the resultant load of these compounds, normally buffered by the cell, becomes toxic. Studies are being done to assay the effectiveness of drugs thought to scavenge the free radicals and to inhibit the production of thromboxane and leukotrienes. Controversy and conflicting claims surround the results of these studies.

These new strategies, especially those dealing with calcium homeostasis, hold great promise for the management of acute stroke, suggesting that previous therapeutic strategies aimed at treating the circulation may be missing the target: the tissue.

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Vitamin E Use in Neurology

VITAMIN E DEFICIENCY was for many years thought not to occur in humans. Several deficiency states have recently been recognized, however, and some diseases once thought to be untreatable have now been found to be treatable by supplementing vitamin E.

Vitamin E is a fat-soluble substance abundantly present in a normal diet. It is most plentiful in vegetable oils and whole grains, but it is also present in green plants and meat and dairy products. The minimum daily requirement is 8 to 10 mg per day, although patients on total parenteral nutrition require about 50 mg per day. Dosages of as much as 100 to 200 mg per kg body weight per day orally or 1 to 2 mg per kg per day intramuscularly are used to treat deficiency states due to malabsorption. Normal serum levels are between 0.5 and 2.0 mg per dl (0.011 mmol per liter). It is probably more meaningful, however, to measure vitamin E levels relative to the level of total lipids (normal greater than 0.6 mg per gram of lipid), as patients with vitamin E deficiency with normal absolute levels but low relative levels have been reported. Vitamin E works together with selenium to prevent superoxides from peroxidating polyunsaturated lipids in cell membranes.

The clinical syndrome associated with vitamin E deficiency usually resembles a spinocerebellar degeneration with ataxia, hyporeflexia, a loss of proprioception, and sometimes cerebellar tremor. Other manifestations are pigmentary retinal degeneration with or without visual loss, dysarthria and dysphagia, ophthalmoplegia, and dystonic

posturing. Patients with Friedreich's ataxia and Charcot-Marie-Tooth disease have normal levels of vitamin E, but those with Charcot-Marie-Tooth disease have been reported to benefit from pharmacologic doses of this vitamin. Vitamin E deficiency has also been associated with extensive morphologic change in muscle, usually without significant clinical weakness.

Because vitamin E is so abundant in a normal diet, dietary deficiency is almost unheard of, and deficiency is usually due to malabsorption. Such malabsorption diseases include chronic cholestasis, cystic fibrosis, the blind loop syndrome, short bowel, intestinal lymphangiectasia, and familial abetalipoproteinemia (the Bassen-Kornzweig syndrome). More recently a number of cases, often familial, of vitamin E deficiency have been found in the absence of a generalized impairment of fat absorption. It has been postulated that these patients have defective hepatocyte transport and release of vitamin E in newly synthesized lipoproteins.

Vitamin E has also been used as an antioxidant in the absence of deficiency, where its effectiveness is less well established. Some of these uses include preventing muscle cramps, preventing intraventricular hemorrhage in premature newborns, attempting to modify or reduce cellular damage caused by ischemia, reducing vasospasm from subarachnoid blood, and treating tardive dyskinesia. The use of vitamin E is also being studied in the treatment of Parkinson's disease on the theory that vitamin E might block a toxin postulated to be responsible for parkinsonism.

In summary, any patient with fat malabsorption, with clinical features resembling those of spinocerebellar degeneration, or with a pigmentary retinopathy should have a workup for possible vitamin E deficiency. Early treatment is important because patients may have early damage to the central nervous system even before symptoms develop, and once symptoms do develop, they are often not completely reversible by administering vitamin E.

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Diagnosing Duchenne Muscular Dystrophy

DUCHENNE TYPE MUSCULAR DYSTROPHY (DMD) is an X-linked recessive disorder characterized clinically by progressive proximal muscular weakness appearing at ages 3 to 5 years. A subsequent loss of muscle strength leads to wheelchair confinement by 11 to 12 years of age and early death due to respiratory failure. Duchenne type muscular dystrophy affects approximately 1 in 3,500 males. About 30% of cases appear to represent new mutations. Previously the diagnosis has been based on high concentrations of soluble muscle-specific enzymes, histologic evidence of widespread muscle degeneration and regeneration with fibrosis, a typical clinical course, and the family history. Two new techniques have recently been developed that permit a more specific diagnosis in both affected persons and carriers.

The DMD gene has been localized to the short arm of the X chromosome, band 21 region by studying affected persons who have other genome defects located in the same region. Using a technique known as restriction fragment length polymorphisms, a marker near the DMD gene was located; other diagnostic DNA probes within the DMD gene have since been identified. Prenatal diagnosis in women at risk is possible, with the test being informative in as many as 96% of women early in pregnancy. Later in pregnancy, the technique can be used on fetal tissue obtained with amniocentesis. These DNA probes now permit increased accuracy in genetic counseling and are most useful in detecting female carriers.

The entire gene has been cloned, and preliminary genomic organization is known. The gene is about 2 million base pairs with a high frequency of deletions. The gene product is a newly identified structural protein called dystrophin that represents about 0.001% of normal muscle protein. Dystrophin is less than 3% of normal levels in DMD phenotypes, low in the intermediate or outlier phenotypes, and of normal amount but of abnormal molecular weight in the Becker phenotype. In the near future, patients suspected of having either Duchenne or Becker's muscular dystrophy can be diagnosed with a muscle biopsy and an analysis of the dystrophin content.

While an accurate diagnosis of affected persons and carriers is now possible, the treatment of the disease remains unsatisfactory. The use of prednisone is being investigated, while recent experimental work in dystrophic chickens suggests that pure glucocorticoids such as dexamethasone may be more effective. These agents should be restricted to the experimental setting until the results of clinical trials now in progress are available.

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Recreational Drugs and Stroke in Young Adults

THE EPIDEMIC OF DRUG ABUSE in our country has led to the reappearance of drug-related neurologic complications. If reports in the medical literature are used as a guide, it appears that the number of patients with drug-induced cerebral infarction or hemorrhage has been increasing over the past five years. In fact, drug abuse should be considered one of the more likely causes of stroke in these patients. Most of the popular street drugs, including cocaine, heroin, amphetamine ("speed"), and phencyclidine hydrochloride (PCP), have been implicated, and the types of strokes they cause may have devastating consequences. Moreover, stroke is only one of a number of severe neurologic catastrophes, such as toxic coma and status epilepticus, that may result from drug abuse.

One such stroke syndrome is intracranial hemorrhage. This may be due to rupture of an underlying vascular anomaly—that is, a berry aneurysm or arteriovenous malformation—or it arises from a vessel having no obvious preexisting abnormality. The hemorrhage usually occurs within

minutes to hours after administering the drug (most often cocaine), and the clinical presentation is similar to that seen with "spontaneous" rupture of vascular malformations. The hemorrhage presumably results from the extreme hypertension and changes in vessel tone that result from the sympathomimetic properties of the drugs, although a direct effect of the drugs on vessel integrity has not been excluded.

Nonembolic cerebral infarction is associated primarily with amphetamine and cocaine abuse. Amphetamine may cause a diffuse angiitis of large vessels that appears as arterial "beading" on cerebral angiography. Cocaine use may also cause major vessel occlusion, although we have seen a few cases of infarction limited to the thalamus and midbrain, and there has been one report of the anterior spinal artery syndrome. There has yet to be a well-documented, unequivocal case of cocaine vasculitis, and it seems more likely that cocaine induces vessel thrombosis or focal spasm analogous to that seen in cases of cocaine-associated myocardial infarction.

Cardiocerebral embolus continues to be seen in cases of bacterial endocarditis due to intravenous drug abuse. Patients are also at risk of the rupture of mycotic aneurysms and subsequent subarachnoid or intracerebral hemorrhage, as well as the development of cerebral abscesses. Prolonged intravenous antibiotic therapy remains the mainstay of therapy.

These various stroke syndromes might be predicted to be more common with habitual heavy abuse and to depend on the route of administration. Our experience and that of others suggest this is not the case. Other than strokes associated with bacterial endocarditis, these syndromes have been seen in both first-time users and long-term abusers and by various routes—ingestion, inhalation, "snorting," and intravenous administration. Furthermore, street drugs are often mixed with or replaced by other compounds, such as lidocaine hydrochloride, that have their own neurotoxic effects.

Given the ongoing popularity of recreational drugs, practitioners need to consider drug abuse high on the list of potential causes of a stroke in a young person, and a drug screen should be a routine part of the workup. Programs aimed at prevention need to emphasize both the severe neurologic consequences and the extreme unpredictability that drug abusers face.

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Diagnosis and Treatment of Neurocysticercosis

THE RECENT INCREASE IN IMMIGRATION from Mexico and other cysticercosis-endemic countries has increased the prevalence of neurocysticercosis in the United States. Patients may present with seizures (60%); increased intracranial pressure with headache and papilledema (25%); an altered mental state with dementia and confusion (17%); focal neurologic findings with hemiparesis, paraparesis, and aphasia (12%); or no signs and the condition accidentally discovered (5%). A clinically useful classification system divides neurocysticercosis into active disease with cysticerci that are living or in the process of dying and inactive disease with cysticerci that are old and dead. The types of active disease include brain or spinal cord parenchymal cysts, arachnoiditis with or without hydrocephalus, brain infarction due to vasculitis, and mass effect due to a large cyst or cyst clumps. The types of inactive disease include brain parenchymal calcifications from dead cysticerci and hydrocephalus due to meningeal fibrosis.

The diagnosis of neurocysticercosis is most often made by computed tomography (CT). A CT scan in patients with active disease often shows one or more 5- to 20-mm diameter parenchymal cysts that may or may not show contrast enhancement of the cyst ring or hydrocephalus. Because intraventricular and subarachnoid cysts are often isodense with cerebrospinal fluid, they are difficult to recognize by CT. Nonionic contrast CT ventriculography may be needed to outline them. Early acute cysticercosis encephalitis may show diffuse brain swelling with or without multiple tiny foci of increased density representing the scoleces within cysticerci. A CT scan in patients with inactive disease often shows multiple 2- to 6-mm diameter scattered calcifications and occasionally hydrocephalus.

Magnetic resonance (MR) imaging in active disease shows both parenchymal and ventricular cysticerci as cysts with MR signal properties paralleling cerebrospinal fluid. Within the cyst a high-intensity 2- to 4-mm mural nodule containing the scolex may be seen. Administering gadolinium may show ring enhancement of the cyst. Dying cysts may be surrounded by a high-intensity rim of tissue edema. Racemose cysts in the subarachnoid space are larger and lack a mural nodule. Dead calcified cysts are difficult to recognize by magnetic resonance.

The detection of antibody against cysticercus antigens as measured by the enzyme-linked immunosorbent assay (ELISA) in the cerebrospinal fluid of patients with active disease has a sensitivity of more than 80% and a specificity of more than 90%. In serum the ELISA test has a sensitivity of 70% and a specificity of 50%. The Parasitic Disease Branch at the Centers for Disease Control, Atlanta, has developed a new immunoblot test that appears to have a sensitivity and specificity of close to 100%. False-negative tests occur most often in patients with few parenchymal cysts or inactive disease. Serologic tests appear to be most helpful in evaluating unexplained chronic meningitis or large atypical cysts. A biopsy of cysticercus subcutaneous lesions can provide a definitive diagnosis.

A regimen of praziquantel, 50 to 75 mg per kg body weight per day in three divided doses orally for 15 days, is effective against living parenchymal cysts. Praziquantel is well absorbed from the gut, and free praziquantel in the serum rapidly enters CSF and cyst fluid. The drug is well tolerated, with the main side effects being gastrointestinal symptoms, headaches, and a decreased sense of well-being. Dexamethasone, 12 to 24 mg a day, or prednisone, 40 to 60 mg a day, is often given with praziquantel to reduce the transient worsening of neurologic signs or seizures that may accompany treatment. Praziquantel treatment cures or produces improvement in about 90% of patients with parenchymal cysts but in only about 50% of patients with arachnoiditis. In patients whose condition does not improve, retreatment should be considered with another regimen of praziquantel or with albendazole, 15 mg per kg per day in three

divided doses by mouth for 30 days. Albendazole, a new drug not yet approved by the Food and Drug Administration, appears to be effective and also has few side effects. Inactive disease appears not to be affected by anticysticercosis therapy. Hydrocephalus often requires ventriculoperitoneal shunting.

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Thrombolytic Therapy for Acute Stroke

THROMBOLYTIC THERAPY FOLLOWING ACUTE STROKE is currently not recommended owing to the risk of cerebral hemorrhage. Clinical investigations before the computed tomographic (CT) scan era indicated that acute thrombolysis with exogenous agents such as streptokinase or urokinase promoted cerebral hemorrhage and clinical deterioration in patients with stroke. The difficulties encountered with those agents may have been due to several problems: the lack of CT to rule out intracerebral hemorrhage before treatment; an inadequate control of blood pressure; and the peripheral depletion of fibrinogen due to these thrombolytic agents, resulting in an anticoagulated state.

The development of recombinant manufactured tissue plasminogen activator (tPA) has reawakened an interest in using thrombolysis after an acute stroke. Tissue plasminogen activator does not promote a systemic lytic state as it is fibrin-specific; it is active on plasminogen only if bound to fibrin on the surface of a clot. Tissue plasminogen activator has a short half-life so that the thrombolytic effect can be controlled using a peripheral intravenous infusion. Intra-arterial infusions are not necessary with the use of tPA as it is clot-specific.

To date, several necessary studies in animals to assess the safety and efficacy of tPA have been completed. Tissue plasminogen activator has been shown to effectively lyse emboli in the cerebral circulation of rats and rabbits. Thrombolysis as late as eight hours after a cerebral occlusion in animals is not associated with an increase in the incidence or size of cerebral hemorrhagic infarction. Administering tPA to animals within 45 minutes of cerebral ischemia appears to be effective in restoring neurologic function. Thus, from these preliminary studies, it appears that it is both safe and effective if administered promptly after a stroke occurs.

Clinical trials of the use of tPA are currently underway. The goal is to establish a safe dose to use in randomized double-blind studies of efficacy. Although there is great promise that ultimately tPA will be effective in patients with acute stroke, at present its use is restricted to the context of a research trial. In the large trials of administering tPA for coronary thrombosis, higher doses are reportedly associated with an increased incidence of cerebral hemorrhage compared with lower doses. It is not yet clear whether these observations are accurate or what implications these findings have in the design of trials of tPA use for acute stroke.

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Editorials

On Dismemberment of the Corpus of Medicine

THESE ARE TIMES OF STRESS on the corpus of medicine and of the medical profession that are probably unprecedented. The forces pointing toward fragmentation and perhaps to dismemberment are strong, and this at a time when the need to preserve and even strengthen the unity and integrity of the profession is as great as it ever has been. The most recent challenge is the Harvard Resource-Based Relative Value Study (RBRVS), which would alter the ways physicians in some specialties are paid, to the advantage of some and to the disadvantage of others. Already, some who consider themselves disadvantaged by the study's findings are seeking ways to protect themselves, whether or not this might be to the advantage or disadvantage of their colleagues or the profession as a whole. When the issues are such that they threaten to affect the pocketbook, protectionist action is natural and understandable. But to the extent that these actions are precursors to more serious fragmentation or even some further dismemberment of the corpus of the medical profession, there may be a larger duty.

Dismemberment is nothing new to the medical profession. Long ago, dentists and apothecaries went their own ways. More recently, there are optometrists, podiatrists, and psychologists, for example, each with their own professional membership and organizations that exist outside the corpus of the medical profession. Nursing is now a fully recognized profession with major responsibilities in patient care; yet it is outside the corpus of the medical profession. The fact is that there are many specialized health professionals who perform specialized roles in patient care who are not members of the corpus of medicine. While all of this may not strictly be dismemberment, nevertheless each has separated a segment of the whole of patient care, and one can think of these professions as separated members of the corpus of the medical profession. And, for better or for worse, each of these separate segments is seeking to expand its scope of practice within what has been the corpus of medicine.

But the corpus of medicine is also being fractionated from within. Medical science has necessitated first, specialization, and more recently, further subspecialization within the specialties of medicine. Already this is having profound effects upon the profession and upon patient care, some good and some not so good. The good is that subspecialists can master and render the most up-to-date care in the fields of their special expertise, and the not so good is that what are really whole patients may in effect become dismembered to receive specialized care for their various ailing parts, sometimes with little attention to the whole person who suffers illness that, like the whole person, may be greater than the sum of its parts. And a curious by-product of this fractionation is that as physicians specialize, they reduce rather than expand their scopes of practice within the corpus of medicine with effects on the whole that remain to be seen.

Fractionation and dismemberment both give rise to special interests and a loss of a sense of the whole of which all are a part. Special interests tend to express themselves in terms of turfs and pocketbooks, and this can be destructive to the whole. In fact, it has been shown elsewhere in the world that the whole of the medical profession can be brought to its knees if special interests can be successfully pitted against one another. The house of medicine in this nation is now at genuine risk. Fractionation and dismemberment are already very real, and the trends are toward further fractionation and dismemberment. A countervailing force must be sought and brought to bear if the profession is not to be further weakened and its traditional role assumed by others.

Perhaps such a countervailing force is to be found in a return to basics of what medicine is all about—that is, the personhood of patients, the effect of illness on a patient, and the care and treatment given to the whole patient who is ill and in need of help. Just as each patient is a oneness, the corpus of medicine and of the medical profession should be kept as whole as possible, so that its oneness can match the whole of the oneness of a patient who is sick, injured, worried, in pain, or mentally disturbed. The road to further fractionation and progressive dismemberment of the corpus of medicine cannot be healthy for patients, for the medical profession, or, in the long run, for the society that is served. The need is to recapture the oneness, the wholeness, and the leadership in health care in the face of special interests from whatever source.

MSMW

HTLV-I-Associated Diseases

SARA NEELY, MD, presents an excellent overview of the clinical features of some of the illnesses produced by the human T-lymphotropic virus type I (HTLV-I) in this issue of the Journal. The excellent review of the literature also stimulates many unanswered questions that must be addressed in coming years. Additionally, other illnesses produced by this virus and ways to prevent the spread of the virus need to be considered.

The most dramatic syndrome produced by this type C RNA retrovirus is adult T-cell leukemia-lymphoma (ATLL). As reviewed by Neely, ATLL is a high-grade T-cell lymphoma characterized by a rapidly fatal progressive course with widespread involvement of visceral organs, opportunistic infections, the frequent occurrence of a hypercalcemic paraneoplastic syndrome, and a rapid progression to drug resistance. Major unanswered questions regarding this clinical syndrome include defining the exact lymphokine responsible for the paraneoplastic hypercalcemia and ways to treat the disease and its complications. Several lymphokines have been postulated to be the responsible agent causing the osteoclast activation, bone demineralization, and hypercalcemia. At present interleukin 1α (IL-1) appears to be the most likely factor responsible for this syndrome,[1] though this has not been proved conclusively. Proof will require establishing that the malignant cells from hypercalcemic patients produce and secrete more IL-1 than malignant cells from patients without this syndrome. The hypercalcemia is often difficult to control with standard agents but generally clears when an antitumor response has been achieved. The mere presence of hypercalcemia has an adverse effect on survival.[2] Other poor prognostic factors, including a high leukocyte count, a high serum lactic dehydrogenase level, and advanced age, have been established.[3] Serum levels of interleukin-2 receptors may also have prognostic importance and may be a marker of

disease activity.[4] The diagnosis of ATLL can be established by showing the existence of a malignant disorder of mature helper T cells with interleukin-2 receptors, monoclonally rearranged T-cell receptors, and the HTLV-I genome in infected T cells. The presence of the HTLV-I genome can be detected with as few as one cell in a million using the polymerase chain reaction.[5]

The major treatment-related issues are ways to combat drug resistance, opportunistic infections, and the underlying HTLV-I infection. Intensive combination chemotherapy produces rapid tumor reduction with palliation of visceral lesions and hypercalcemia in most instances. A rapid outgrowth of drug-resistant clones is common, however, and most often occurs in less than two years. More experimental forms of treatment include the anti-Tac monoclonal antibody used alone or conjugated to toxins or radioisotopes.[6-8] Antitumor effects have been observed with this form of therapy, but the cytoreduction has been modest to date. Deoxycoformycin, an inhibitor of adenosine deaminase, has also been reported to have activity in isolated cases.[9] Opportunistic infections occur with nearly the same frequency as in patients with the acquired immunodeficiency syndrome (human immunodeficiency virus or HTLV-III infection) and require the same means of treatment. Azidothymidine (AZT) and other antiviral agents have not received extensive trials to date. This will certainly be required as patients are likely to do poorly with any form of treatment unless the underlying infection is cleared.

The HTLV-I virus appears to be transmitted through contaminated blood, sexual contact, and at childbirth. The frequency of infected blood in the United States is low, 0.025% in one series.[10] Evidence suggests that HTLV-I is not a new virus and has infected people in the United States for 50 to 100 years. Yet, it is not certain whether the frequency is stable or increasing. At present, blood products are not routinely screened for HTLV-I. Several large studies are in progress to evaluate its frequency in blood products.[11] The results of these studies are eagerly awaited since the consequences are great, but routine screening would add several dollars to the cost of each unit of blood.

After exposure to HTLV-I infection, antibodies may develop, and patients may remain clinically free of disease, or a preleukemia, smoldering leukemia, a chronic subacute form of ATLL, or a progressive neurologic disease may develop. Less than 5% of infected people appear to have one of these illnesses, and they may develop over several decades. It is not clear how most infected people are protected from major illness, why these prodromal syndromes develop in some, and why the full-blown ATLL syndrome develops in a small minority. It is also unclear why and how subacute forms transform into the rapidly fatal ATLL. The prodromal forms of this illness are not treated as patients are generally asymptomatic and there is no effective treatment. The disease can only be detected in peripheral blood T cells in these patients at this point. Antiviral agents need to be evaluated in these patients to determine if they can clear the infection and prevent progression to ATLL.

There is evidence that HTLV-I may infect the central nervous system and cause a tropical spastic paraparesis sometimes referred to as HTLV-I-associated myelopathy (HAM).[12-14] This appears to be quite common in the Caribbean region and is characterized by a slowly progressive neurologic disease that causes weakness in the legs and lower body. Immunologic and pulmonary problems may also develop.[15] Neurologic diseases may occur because the virus binds to the same receptor on helper T cells and cells in the central nervous system. The extent of neurologic illness in the United States caused by HTLV-I is largely undefined.

HTLV-I infection is quite rare in the US, and attempts to develop vaccines for HTLV-I, -II, and -III are being pursued extensively.[16,17] Prevention will likely be more effective in controlling the problem than treatment approaches. It must be hoped that principles that will be established for developing an effective vaccine for any of the HTLV viruses will apply to developing an effective HTLV-I vaccine as well.

The ATLL syndrome was first described in the mid-1970s, and the HTLV-I virus was discovered and isolated by 1978. It is hoped that the advances in biology that allowed for the rapid discovery of the cause of the infection will continue so that the disease can be prevented before it becomes a major health problem in the United States.

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Case Reports

Is *Ixodes (Ixodiopsis) angustus* a Vector of Lyme Disease in Washington State?

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LYME DISEASE is a tick-borne spirochetosis that, since its initial recognition in the mid-1970s, has become a public health problem of increasing concern in the United States.[1-3] It is presently the most commonly reported arthropod-transmitted disease in this country. In the West, human cases have been recorded along the Pacific slope of the Sierra Nevada mountains (California) and in Nevada, Oregon, and Utah.[2] In California alone, 125 indigenously acquired cases were reported by state health authorities in 1986, and the official total for 1987 will be higher (R.A. Murray, PhD, oral communication, April 1988).

Two species of hard-bodied (ixodid) ticks serve as primary vectors of the etiologic agent, *Borrelia burgdorferi,* to humans—that is, *Ixodes (Ixodes) dammini* and *Ixodes (Ixodes) pacificus* in eastern and western United States, respectively.[4,5] A third species of ixodid tick, *Amblyomma americanum,* has been implicated as a secondary vector to humans in New Jersey.[6,7] Although the western black-legged tick, *I pacificus,* is assumed to be the usual source of human infection in the Far West,[5,8-11] other ixodid ticks that bite people less frequently also may transmit the infection to humans in this region. With this communication, we report a case of Lyme disease acquired in Washington State that was associated with the bite of an *Ixodes* tick in the subgenus *Ixodiopsis.* This tick, *Ixodes angustus,* has not previously been incriminated as a vector of *B burgdorferi.*

Report of a Case

The patient, a 3-year-old girl from Redmond, Washington, was referred to one of us (H.F.) in May 1987 for the removal of a tick that was embedded in the lash line of her right upper eyelid (Figure 1). Her parents noted the foreign body two days before the initial appointment and had tried unsuccessfully to remove it. They reported that their daughter had encountered the tick near their home in suburban Seattle. Examination showed an engorged, live tick embedded in the nasal aspect of the right superior eyelid, with bloody excrements on the skin immediately below the eye (Figure 1). A slight erythema had developed on the eyelid around the site of tick attachment. The tick was removed with forceps after the child had been sedated with chloral hydrate. A culture of the wound was taken and topical erythromycin ointment prescribed, to be applied three times a day for two weeks. During a follow-up appointment one week after removal of the tick, the wound was healing uneventfully, though a slight erythema remained (Figure 2). Treatment with topical erythromycin was continued even though the culture of the wound was negative for pathogens.

Three weeks after the tick removal, the patient presented with a notably erythematous skin lesion (Figure 3). Her parents reported that the lesion had been present for six days (beginning 23 days after the initial contact with the tick), with no associated signs or symptoms except that the area was tender to the touch. On biomicroscopic examination, there was a cherry red, swollen area in the upper lid measuring about 5 by 7 mm, extending in a semicircular area around the tick attachment site. The skin was intact and no residual foreign bodies were observed in the eyelid. A second culture of the area showed no growth within 48 hours. The topical antibiotic was switched to a combination ophthalmic ointment containing polymyxin B sulfate, bacitracin zinc, and neomycin sulfate (Neosporin), to be applied three times a day, and cephalexin oral suspension (Keflex), 125 mg three times a day, was prescribed for two weeks. Additionally, the parents were instructed to apply warm soaks four times a day to the affected area. Within the next three weeks, the lesion resolved slowly, and five months later only a slight erythema remained.

The initial clinical impression was that the delayed skin reaction was due either to a granulomatous response to retained mouthparts or to a secondary bacterial infection. (A subsequent examination of the tick by one of us [R.S.L.] showed that the distal portion of the hypostome had broken off; the hypostome is the central-most portion of the mouthparts that serves to anchor the tick to its host while feeding.) On the other hand, the time course and appearance of the skin lesion were also characteristic of erythema migrans (formerly erythema chronicum migrans), the hallmark of Lyme disease.[2,12] Serologic tests for Lyme disease six months after the tick bite showed that the patient had an indirect fluorescent antibody (IFA) titer of 1:256 and an optical density ratio by enzyme-linked immunosorbent assay of 0.27. An IFA titer of 1:256 or greater and an optical density ratio of greater than 0.20 are considered diagnostic of Lyme disease in a patient having compatible clinical features, such as erythema migrans. Serologic tests for syphilis proved to be negative. On receipt of the serologic findings, the patient was treated with a two-week course of oral penicillin V potassium, 125 mg four times a day. To date, she has shown no evidence of arthritis, carditis, neuritis, or other sequelae that may occur during late Lyme disease.[13]

Discussion

Lyme disease was not recognized as a distinct clinical disorder in Washington before 1986. Since then, 11 cases

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have been confirmed among residents of this state. In the West generally, and in California and Oregon specifically, the western black-legged tick, *Ixodes (Ixodes) pacificus,* is thought to be the primary vector of *B burgdorferi.*[5,8-11] This tick has been recorded from 14 of Washington's 39 counties so far by a passive surveillance system. The relation of *I pacificus,* however, and other ticks to the Lyme disease spirochete and its associated vertebrate hosts has not been studied in the Pacific Northwest.

In the northeastern United States, the primary vector of *B burgdorferi* to humans is *I (Ixodes) dammini,*[4] which has a broad host range similar to that of *I pacificus.* Two other tick species in the subgenus *Ixodes, Ixodes neotomae* and *Ixodes scapularis,* also have been found infected naturally with *B burgdorferi* in this country.[14,15] *I neotomae* feeds mainly on lagomorphs and wood rats,[16,17] whereas *I scapularis* attaches to various species of lizards, birds, and mammals (including humans).

The tick implicated in the case described here was determined to be an adult female *Ixodes (Ixodiopsis) angustus.* J. E. Keirans, PhD, of the Smithsonian Institution, United States National Museum, confirmed the specific identity of the tick. This tick has been recorded from at least 24 states, including all of those in the Far West.[16] Its preferred hosts are various species of small rodents, but it occurs sometimes on shrews, cats, dogs, and humans.[16] In Washington State, *I angustus* has been recorded from ten counties, all of which are located west of the Cascade Mountains.

Figure 1.—A female *Ixodes angustus* is attached to the lash line of the right upper eyelid of the patient.

Figure 2.—The eyelid of the patient one week after removal of the tick shows slight erythema.

Ixodes angustus is the first member of the subgenus *Ixodiopsis* to be incriminated as a vector of *B burgdorferi* in this country or elsewhere; the principal vector in Europe is *Ixodes (Ixodes) ricinus,*[18] and *Ixodes (Ixodes) persulcatus* has been implicated recently as a vector in Asia.[19] It is not surprising that a tick such as *I angustus* that bites rodents principally and humans accidentally may sometimes transmit the Lyme disease spirochete to people. The white-footed mouse *(Peromyscus leucopus)* has been shown to be the primary reservoir of *B burgdorferi* in the northeastern US,[20,21] and the deer mouse *(Peromyscus maniculatus)* likewise is susceptible to infection with this spirochete.[22,23] Moreover, *P maniculatus* is distributed throughout most of the continental US including all of the West,[24] and this rodent and several other *Peromyscus* species serve as hosts of *I angustus.*[17,25]

The association of the bite of an *I angustus* tick with the development of an erythema migrans-like lesion 23 days later and a significant serum antibody titer six months afterward strongly suggests that this particular tick had transmitted *B burgdorferi* infection to our patient. Further, the patient had not traveled to another Lyme disease-endemic area, nor was she known to have been bitten by another tick or other potential arthropod vectors during this period. Definitive proof, of course, that *I angustus* is a vector of *B burgdorferi* must await the recovery of this spirochete from a tick that had been removed from a person who subsequently became ill with Lyme disease.

Lyme disease vector surveillance has not existed to a great extent in Washington State. Field and laboratory studies are necessary to identify tick species in the area and to determine the proportions harboring Lyme disease spirochetes. Tick and spirochete surveys conducted in northern California and southwestern Oregon from 1982 to 1984 have shown that the prevalence of spirochetal infections in adult *I pacificus* has ranged from 0.9% to 4.3%.[5,9] The infection rates for *I dammini,* the main vector for *B burgdorferi* in the northeastern United States, are reported as high as 100% in certain localities.[26] Investigations are underway to determine the prevalence of *B burgdorferi* in *I angustus* and to define the role of this tick in the ecology of Lyme disease.

The association of a Lyme disease case with a species of tick not previously known to be a vector of the disease portends expanding public health problems. *Ixodes angustus* is

Figure 3.—An erythematous lesion is seen on the right upper eyelid three weeks after the tick was removed.

widely distributed in North America, occurring from California to Alaska on the Pacific Coast. Studies on the distribution of ticks in western Oregon have shown that *I angustus* is the most common tick found in certain coastal regions of this area.[27] Although generally considered to be a nest-specific parasite of rodents and insectivores, *I angustus* is known to bite humans.[17] The wide distribution and common occurrence of this tick species may have important implications for potential Lyme disease transmission outside known endemic areas and an increased incidence within established areas. Furthermore, as our rural population expands and participation in outdoor recreational activities increases, placing humans into areas formerly the domain of wild animals and their parasites, exposure to ticks and tick-borne diseases will increase.

The transmission of Lyme disease spirochetes to humans may be minimized by the prompt and proper removal of a tick vector. The lengthy feeding period (several days) is an important factor contributing to the risk of infection.[28] In addition to timely removal, it is important that the mouthparts of an embedded tick be removed completely to prevent the occurrence of secondary bacterial infections. The procedure recommended for removing an attached tick is to grasp it as close to the skin surface as possible with forceps or protected fingers and gently pull backward with steady, even pressure.[29]

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Adrenal Apoplexy Revisited

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DESPITE ITS INFREQUENCY, acute adrenocortical insufficiency is an important disorder to recognize because it is uniformly fatal unless promptly treated. Acute adrenocortical insufficiency is brought about by an intense stress occurring either in a patient with preexisting chronic adrenocortical insufficiency or in a patient with presumably normal adrenal glands that undergo massive hemorrhagic necrosis. This latter condition has been termed adrenal apoplexy. I describe the cases of two patients with adrenal apoplexy and discuss the cardinal aspects of its pathogenesis, clinical diagnosis, and management.

Report of Cases

Case 1

The patient, a 74-year-old woman, was admitted to the medical service because of fever, cough, shortness of breath, and chest pain for a week that had not responded to erythromycin therapy. She had had a resection of an adenocarcinoma of the sigmoid colon four years earlier without evidence of recurrence, a cerebrovascular accident six years earlier, and cutaneous lupus in the remote past at which time she was given glucocorticoids for three months. She was taking isosorbide dinitrate for mild angina and hydrochlorothiazide and triamterene for hypertension. On physical examination she was in moderate respiratory distress with a heart rate of 100 beats per minute, a blood pressure of 145/80 mm of mercury, a temperature of 38.3°C (101°F), a respiratory rate of 26 per minute, and signs of left lower lobe consolidation; the rest of the examination was unremarkable. A chest roentgenogram showed bilateral patchy infiltrates. Examination of a sputum specimen showed leukocytes and a mixture of bacteria that on culture yielded *Hemophilus influenzae* and oral flora. The blood leukocyte count was 8.1×10^9 per liter with 0.66 polymorphonuclear leukocytes and 0.17 band forms.

Treatment with intravenous fluids and cefamandole nafate was begun. On the fourth hospital day, the patient began

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to have vague abdominal discomfort accompanied by nausea and occasional vomiting. These persisted, and despite clearing of the pulmonary infiltrates she continued to have daily temperature spikes to 39°C (102°F). She became progressively weaker and more lethargic. On the ninth hospital day, blood cultures showed no growth and the blood leukocyte count was 5.9×10^9 per liter with a normal differential. On a serum electrolyte panel, the sodium level was 122 mmol per liter and the potassium was 4.9 mmol per liter. Over the ensuing five days, the blood pressure ranged around 100/60 mm of mercury and the lethargy, nausea, and daily temperature spikes persisted. On the 14th hospital day, she had a cardiac arrest from which she was initially resuscitated, but despite maximal support with pressors, hypotension persisted and she died.

A necropsy examination disclosed organizing bilateral pneumonitis, extensive infiltration of para-aortic lymph nodes by adenocarcinoma similar in histopathologic appearance to the previously resected colonic carcinoma, and extensive hemorrhage within both adrenal glands (Figure 1). On histopathologic examination of both adrenal glands, there was extensive hemorrhagic necrosis with thrombi in the adrenal vein and its tributaries but no evidence of metastases.

Case 2

A 69-year-old man was admitted to the medical service because for ten days he had had weakness, intermittent nausea and vomiting, mental confusion, and fever. Two weeks earlier he had undergone right- and left-sided catheterization of the heart that apparently was uncomplicated. For three years he had had congestive heart failure accompanied by intermittent atrial fibrillation. His blood pressure, reportedly, was always in the range of 130/80 mm of mercury. He had not taken glucocorticoids. He was taking verapamil hydrochloride, 80 mg three times a day.

Figure 1.—The transected adrenal gland of patient 1 shows a central hematoma (courtesy of Harvey Z. Klein, MD, Department of Pathology and Laboratory Medicine, Mount Zion Hospital and Medical Center).

On physical examination he was lethargic with a blood pressure of 110/70 mm of mercury while supine that fell to 100/60 mm of mercury on sitting, a temperature of 38°C (100.4°F), and cardiomegaly with a systolic ejection murmur along the left sternal border; there were no signs of congestive heart failure. Specimens of blood, urine, and cerebrospinal fluid were cultured, and treatment with penicillin, nafcillin sodium, and tobramycin was begun for a presumed infection. There was no growth on the cultures after three days, and the antibiotic therapy was withdrawn. The fever and lethargy persisted, however, and because of a serum sodium level of 123 mmol per liter and a potassium level of 4.6 mmol per liter, a cosyntropin stimulation test was done. The serum cortisol level was 110 nmol per liter (4 μg per dl) before and 140 nmol per liter (5 μg per dl) one hour after cosyntropin was administered. Accordingly, an intravenous infusion of hydrocortisone was begun and within 12 hours the fever and lethargy had disappeared and the blood pressure had risen to 130/80 mm of mercury. A computed tomographic scan of the abdomen showed massive enlargement of both adrenal glands consistent with hemorrhage. Treatment with oral hydrocortisone and fludrocortisone acetate was instituted, and at the time of discharge his blood pressure and serum electrolyte values were normal.

Discussion

In several large necropsy series, the incidence of adrenal apoplexy—that is, massive adrenal hemorrhagic necrosis—ranged between 0.16% and 0.69%.[1-5] These figures, however, underestimate the true incidence of adrenal apoplexy because in the series cited, the denominator was not restricted to patients dying of shock or in whom death was sudden and unexpected. Thus, the diagnosis is still often left to a pathologist, as exemplified by the case of patient 1. On the other hand, in the case of patient 2, even though the antecedent stressful insult appeared minor, prompt diagnosis and therapeutic intervention led to full recovery.

The clinical setting in which adrenal apoplexy usually occurs is that of stress accompanying a major insult, such as severe infection, a perforated viscus, trauma, burns, eclampsia, or a cardiovascular catastrophe. Anticoagulant therapy is an occasional contributing factor.[2] It has also been reported to occur as a complication of treatment with adrenocorticotropin (ACTH).[6] At necropsy, the adrenal glands present a characteristic appearance consisting of a central hematoma enveloped by a rim of residual cortex and of thrombosis of the adrenal vein and its tributaries.[1] These features were present in the case of patient 1 (Figure 1).

The pathogenetic mechanism underlying adrenal apoplexy is still enigmatic. It may be sought, however, in the unique vascular anatomy and special functional characteristics of the adrenal gland. Several authors[4,7] have drawn attention to the fact that the adrenal gland is endowed with an exceptionally rich arterial blood supply that increases remarkably during stress. By contrast, venous drainage is limited to thin-walled venous sinuses that drain into a single vein. A fairly consistent finding in the adrenal gland that is the seat of hemorrhage is the presence of thrombi in the adrenal vein and its tributaries.[1,3,4,7,8] It has been suggested

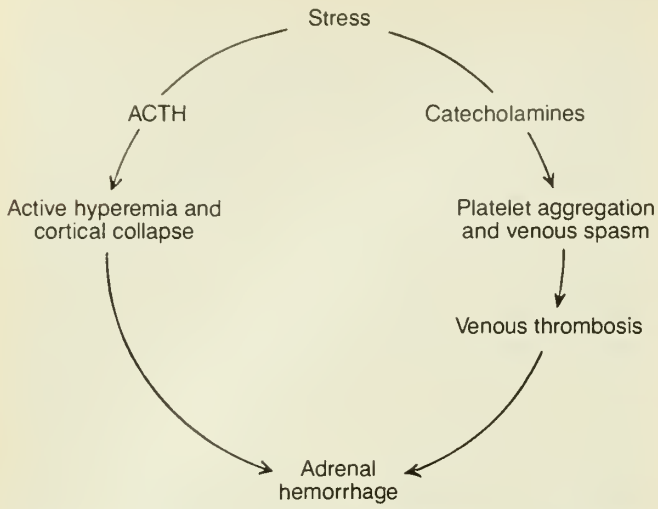

Figure 2.—The schema shows the putative pathogenetic interplay that leads to adrenal hemorrhage.

that the high concentrations of cortisol and catecholamines in the adrenal venous effluent during stress induce venous spasm and platelet aggregation, thereby leading to thrombus formation.[8] Moreover, ACTH stimulation of the adrenal gland during stress leads to hyperemia and to lipid depletion that favors cortical collapse. In this regard, it is noteworthy that adrenal apoplexy may follow treatment with exogenous ACTH.[6] Thus, the interplay of all the foregoing factors might ultimately result in adrenal hemorrhage (Figure 2). Indeed, the characteristic gross pathologic finding of a massive central hematoma is entirely consistent with this pathogenetic interplay.

The clinical presentation is nonspecific.[4] Accordingly, acute adrenocortical insufficiency resulting from adrenal apoplexy should be considered in any patient in whom hypotension or vascular collapse supervenes unexpectedly or whose condition does not respond to the usual supportive measures. Vomiting and abdominal discomfort may occur and in some instances be severe enough to mimic a surgical acute abdomen. Occasionally, adrenal apoplexy may be accompanied by flank or back pain. The presence of hyponatremia in association with azotemia should enhance one's index of suspicion although hyponatremia is not a consistent feature, and hyperkalemia is often not present.[9] As exemplified by the case of patient 2, a computed tomographic scan of the abdomen would suggest the presence of adrenal apoplexy if bilateral adrenal enlargement were found.[10]

The diagnosis of acute adrenocortical insufficiency in an acutely ill patient is readily established by measuring the serum cortisol level. In this circumstance, a value that is not clearly increased strongly suggests a diminished adrenocortical reserve, and a diminished or absent response to cosyntropin would provide absolute confirmation. Once a blood specimen has been collected, treatment with intravenous hydrocortisone in a dosage of 200 mg to 300 mg during the first 24 hours should be instituted. Such an approach would salvage patients from a life-threatening disorder that is eminently treatable if recognized early.

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Postpartum Immunologic-Mediated Pulmonary Edema Associated With Transfusion of Blood Containing an Anti-B-Lymphocyte Antibody

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POSTTRANSFUSION IMMUNOLOGIC-MEDIATED PULMONARY EDEMA is a condition of acute respiratory failure that is most frequently caused by an antibody in donor blood that has a specificity toward an antigen found on patient granulocytes, lymphocytes, or both.[1] We describe here a postpartum case in which low-dose steroid treatment led to a dramatic improvement in oxygenation.

Report of a Case

The patient, a 24-year-old woman, gravida 3, para 2, was admitted at 37½ weeks' gestation with placenta previa. Her medical history was notable for heroin abuse, and she was now on methadone maintenance. Admission laboratory values included a leukocyte count of 11.4×10^9 per liter, a hematocrit of 0.28, and a platelet count of 204×10^9 per liter. The admission differential included 0.74 segmented polymorphonuclear leukocytes, 0.01 band forms, 0.01 metamyelocytes, 0.10 eosinophils, 0.11 lymphocytes, and 0.03 monocytes. A test for the hepatitis B surface antigen was negative.

The patient underwent a cesarean section with an estimated blood loss of 1,500 ml, and she was given a transfusion of two units of erythrocytes. While in the recovery room, she had tachypnea, tachycardia, and hypotension with a blood pressure of 85/44 mm of mercury. On examination of the lungs, there were no rales. Blood gas determinations done with the patient breathing 6 liters of oxygen by mask indicated a Po_2 of 5.86 kPa (44 mm of mercury), a Pco_2 of 4.26 kPa (32 mm of mercury), a bicarbonate of 22 mmol per

(Newman RS, Williams JH, Moberg LJ, et al: Postpartum immunologic-mediated pulmonary edema associated with transfusion of blood containing an anti-B-lymphocyte antibody. West J Med 1989 May; 150:584-586)

From the Departments of Pathology (Dr Newman and Ms Cook), Medicine (Dr Williams), Obstetrics and Gynecology (Dr Moberg), University of California, Irvine, California College of Medicine, Irvine, and the University of California, Irvine, Medical Center, Orange, California.

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liter, and a pH of 7.42. An endotracheal tube was introduced, a dopamine infusion was started, and a Swan-Ganz line was placed. Her pulmonary wedge pressure was 7 mm of mercury, and a chest x-ray film was interpreted as showing extensive patchy alveolar consolidation throughout both lung fields with a slightly increased heart size. She had a prothrombin time of 13.3 seconds (normal < 12.8), an activated partial thromboplastin time of 41.6 seconds (normal <37.8), a fibrinogen level of 1.8 grams per liter, a platelet count of 158×10^9 per liter, and fibrin degradation products of 40 to 80 mg per liter. The differential diagnosis at this point included amniotic fluid embolism and immunologic-mediated pulmonary edema; pulmonary embolism was considered but felt to be much less likely. A blood specimen was obtained from the Swan-Ganz catheter for cytologic examination for squamous cells and for a lymphocyte crossmatch with donor serum.

Eight hours after the respiratory distress began, repeat blood gas determinations with the patient breathing 100% oxygen indicated a Po_2 of 10.26 kPa (77 mm of mercury), a Pco_2 of 4.80 kPa (36 mm of mercury), a bicarbonate of 22 mmol per liter, and a pH of 7.40. The patient received an infusion of 1 gram of hydrocortisone for possible immunologic-mediated pulmonary edema, 15 units of cryoprecipitate for possible amniotic fluid embolism,[2] and a loading dose of 10,000 units of heparin for possible pulmonary embolism. Two hours later, the blood gas measurements were repeated and showed a dramatic improvement in oxygenation with a Po_2 of 34.18 kPa (256.4 mm of mercury) with the patient receiving 100% oxygen (Figure 1). Over the next two days, the oxygen flow was lowered to 45%; a total of nine days was required, however, before the patient could be weaned completely from the respirator.

Laboratory Methods

Lymphocytotoxicity Testing

Donor serum was allowed to react with recipient lymphocytes by standard lymphocytotoxicity methods.[3] Human leukocyte antigen typing of the patient was determined by standard lymphocytotoxicity testing with commercially prepared trays of well-characterized antiserum to A, B, C, and DR antigens. Appropriate positive, negative, and autologous controls were included. HLA-A, -B, and -C and HLA-DR antibodies in the donor units were screened for using a panel of 56 and 27 HLA-typed lymphocytes, respectively, selected to cover the spectrum of well-defined HLA specificities.*

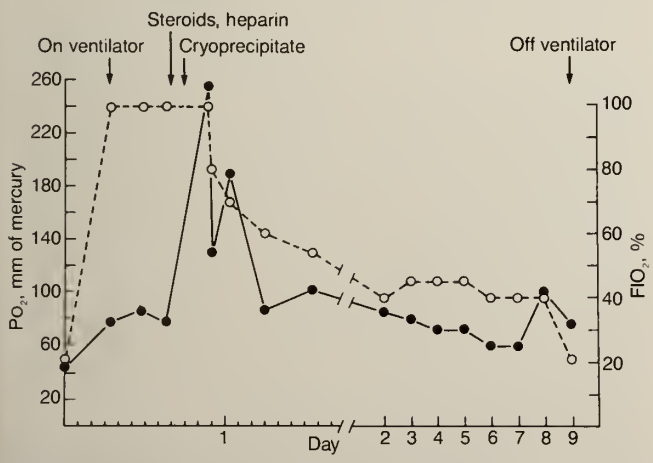

Figure 1.—The graph shows the temporal sequence of the Po_2 (●) and the inspired flow of oxygen (FIO_2; ○) required to maintain an adequate Po_2 after the onset of respiratory distress immediately following a blood transfusion.

Whole Blood Cytology

Blood was analyzed for fetal squamous cells and fat by keratin stains and by hematoxylin and eosin, oil red O, and periodic acid-Schiff stains.[4-6]

Fibronectin

Citrate-anticoagulated plasma was prepared within three hours of the blood collection and stored at −70°C until assayed. Fibronectin levels were determined using a commercially available immunoturbidometric assay (Atlantic Antibody, Scarborough, Maine) on plasma from the patient and from 25 healthy female donors.

Results

Serum from one of the two blood donors was found to be strongly cytotoxic for the patient's B lymphocytes at 37°C. Antibody screening of the cytotoxic serum indicated an anti-DQ1 cell specificity. HLA typing of the patient's B cells indicated the presence of the DQ1 antigen. Analysis of blood drawn from the pulmonary circulation did not indicate the presence of squamous cells, fat cells, or mucin. Fibronectin determination on the patient's plasma before the cryoprecipitate infusion was 220 mg per liter (normal range, 268 ± 74 [1 standard deviation]).

Discussion

Immunologic-mediated pulmonary edema has been estimated to occur with a frequency of about 1 case per 5,000 units of blood transfused,[1] or 1 in 2,500 patients after the infusion of two units of blood products. This frequency contrasts with that of amniotic fluid embolism, which has been estimated to occur between 1 in 8,000 and 1 in 80,000 deliveries.[7] Respiratory difficulty frequently ensues during a transfusion or soon thereafter, although symptoms have been reported to begin as long as six hours after a transfusion.[8] The reaction can occur after the infusion of any blood component, including packed red cells or whole blood,[9] fresh frozen plasma,[10] cryoprecipitate,[11] and, undoubtedly, platelets. The implicated donors are multiparous women[9] who with increasing parity are known to have an increased likelihood of forming antileukocyte antibodies,[12] including those with an anti-HLA specificity.

The morbidity of immunologic-mediated pulmonary edema is striking: 72% of patients require artificial ventilation, and 6% die.[1] Of patients who survive, none have been reported to have long-term sequelae.

Jacob and co-workers have suggested that respiratory difficulty may be due to the interaction of complement fragments, especially C5a, with granulocytes, resulting in a leukosequestration with obstruction of blood flow and the release of granulocyte metabolic products—hydrogen peroxide, superoxide radicals, proteases—that may damage the endothelial barrier.[13] Additionally, complement-activated granulocytes may release membrane lipid-derived products—leukotrienes and thromboxane—that may potentiate edema by causing postcapillary vasoconstriction and increased pulmonary vascular resistance.[14] Direct antibody-

*John Lee, PhD, Head, American Red Cross HLA Laboratory, Bethesda, Maryland, performed the HLA antibody screening.

mediated cytotoxicity of endothelial cells may also play a role as lymphocyte class I and class II HLA antigens are both known to be present on these cells.[15-17]

The diagnosis of this disorder can usually be confirmed by standard HLA lymphocytotoxicity testing[3] that is routinely used by medical centers involved in organ transplantation or the treatment of patients with leukemia. Granulocyte antibody testing techniques may occasionally detect cases of neutrophil-specific antibodies not picked up by HLA testing, but these techniques are not as readily available as HLA testing.

The therapy for this condition has been recommended by some authors to be one to two large doses of corticosteroids (30 mg per kg body weight of methylprednisolone sodium succinate or 90 mg per kg of hydrocortisone), which can inhibit the aggregation of granulocytes with exposure to C5a in vitro,[13,18] as well as inhibit granulocyte production of superoxide radicals and arachidonic acid-derived products.[19] In shock states that may be associated with the adult respiratory distress syndrome in which leukostasis and endothelial damage are common, modest doses of steroids have not been effective in humans. Nevertheless, in this case, a low dosage of about 20 mg per kg of hydrocortisone appears to have been effective. This is not surprising in view of in vitro studies that have shown an effect, though admittedly not as strong, of steroid use at lower concentrations.[18]

Immunologic-mediated pulmonary edema could theoretically be prevented by screening all blood donors for leukocyte antibodies, but because of costs, logistics, and long temporal delays usually associated with leukocyte antibody testing, this is not done routinely. Nonetheless, should a donor's blood be implicated in causing this condition, the erythrocytes should only be administered as washed red cells after future donations, and the platelets and plasma must be discarded.

In summary, in any patient with acute respiratory failure within six hours of a blood transfusion without evidence of congestive heart failure or fluid overload, a diagnosis of immunologic-mediated pulmonary edema must be seriously considered in the differential diagnosis.

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Correspondence

A National Health Program

To THE EDITOR: The political commentary, "Why It's Time for a National Health Program in the United States," by Waitzkin in the January issue[1] reveals that despite the extensive experience of numerous other countries with attempts to provide universal health care, at least among some persons the lessons have not been learned. There is no way on earth that all of the medical needs of an aging society can be covered without limitation. Whether the limitations and rationing are applied randomly by application of financial criteria, as in the United States, or by policy in which particular procedures are denied to particular groups, as in the United Kingdom, some form of rationing has to occur. Dr Waitzkin's article is based on the assumption that there is an entitlement to health care. This is a value judgment that may be imposed on the rest of us by political muscle but has no independent or objective validity. No one has an entitlement to the product of my time and energy or that of any other physician, proposals for national health insurance to the contrary.

Dr Waitzkin may well be correct that such a program is inevitable in the United States; that will not make it either useful, efficient, or an improvement in the long run over the current system.

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REFERENCE

1. Waitzkin H: Why it's time for a national health program in the United States. West J Med 1989 Jan; 150:101-107

* * *

To THE EDITOR: Dr Howard Waitzkin's commentary in the January issue[1] should be required reading for everyone in the health field. It is a blueprint for socialistic diaster! It is hard to believe that an MD, PhD could have reached that august position with no apparent schooling in fundamental economics or civics.

The premise of Dr Waitzkin's assertion is this: "The fundamental assumption of an NHP [National Health Program] is that universal entitlement to adequate health care is a basic human right." I don't agree with that assumption, and I hope, after reading my commentary, that no one else will either.

The problem with granting a "right" to one person is that it *always* takes away a "right" from someone else. Because one right is exclusive of another, we have to be very careful in proclaiming it. For example, if a citizen has an entitlement to adequate health care as a right, those who provide that care *do not* have the right to withhold it. To ensure this "basic human right," the government is charged to see that this care is provided and is also charged with prescribing what and how much care is to be given. This must be done within the government's fiscal restraints, and so the government will also determine how much is to be paid for these services.

What started as a "basic human right" has been at the cost of the patient's individual freedom to choose what is to be done; he or she has abrogated this to the state. The health care provider in the same process has been forced to provide a service for a price determined at the whim of a prodigal government. What before was an honorable profession is now a state of civil servitude. While before the responsibility was to the individual, now the responsibility is to the state.

With socialism, everyone loses. The price is too high; freedom is too precious. Socialistic ombudsmen are quick to assert that the medical profession has become obsessed with financial aggrandizement. They would argue that the true healer is altruistic and that economic discussions are somehow demeaning to the medical profession.

What is a fundamental assertion is that there cannot be individual freedom without economic freedom. Our country and way of life are based on this principle. When a person's worth is dictated by an arbitrary process, that person is a slave. If this can be done to the medical profession, it can be done to all—a mere extension of "basic rights" to include all and, of course, exclude all is true socialistic doublethink.

Adequate health care is not a "basic human right." For that matter, neither is adequate nutrition nor shelter nor everything in life that we as individuals must strive for. In America we call this "the pursuit of happiness." It is not the "gift of happiness."

Dr Waitzkin dedicated his article to the memory of Mr Abe Boxerman, an activist for the rights of senior citizens. I would like to dedicate my commentary to the millions of Americans who have died in many wars for the cause of personal freedom for all, not just senior citizens.

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1. Waitzkin H: Why it's time for a national health program in the United States. West J Med 1989; 150:101-107

* * *

To THE EDITOR: After reading Dr Waitzkin's comprehensive article in the January issue,[1] I passed through several phases of reaction. Hostility went to amusement and ultimately I was left with a subtle, gnawing sense of fear. I imagine the upper middle class citizens in the dying decades of the First Roman Republic may have experienced such real apprehension, as well as the hard-working citizens of capitalist Czechoslovakia in the immediate post-World War II period, when their democracy was subverted and overthrown by socialists backed by the USSR.

The United States is humanity's finest bastion of personal freedom. It is truly the only real deterrent to world socialism (Marxist or by any other name). Our example is closely watched by other countries. Our people are not socialist by nature. All recent elections have demonstrated this fact. Third party (government) redistribution of the wealth is a popular concept in Cuba, Albania, the USSR, etc. It began its infiltration of our democratic/capitalist society during the New Deal of the 1930s. We now have millions of people who are third generation welfare recipients. Many have been crippled morally and emotionally by the welfare system. Our founding fathers designed a magnificent system to permit our citizens to work and to compete. Freedom comes with a price. It also allows one the freedom to fail. "Big Brother" politicians have for years promised other people's hard-earned monies for votes from the members of the less affluent sectors of society. Thank God that this trend was slowed and reversed during the past eight years. When Mr Bush said,

"Read my lips. No new taxes," he was speaking to the large majority of Americans. Americans do not want more of their earnings confiscated by politicians to finance new welfare programs. Jesse Jackson, George McGovern, and Michael Dukakis learned this through the democratic process.

A national health program as proposed by Dr Waitzkin would quickly expand. New bureaus would be set up to enforce government mandates. Overutilization and long waits for care would evolve. Mediocrity would be encouraged. The "smarter bears" would seek other fields. We would in fact move into a level of care akin to socialist countries.

A national health program would be run by bureaucrats. Bureaucrats do not answer to the people directly (witness the excesses of the directors of the FBI, CIA, IRS, etc.). The people would lose a considerable measure of freedom. A national health program would probably demand that all levels of medical care be equal. Medical care would be on the "everyone is entitled to a Mercedes" concept. What would really happen (as has happened in England) is that nobody would get Mercedes care and most of the time everyone would get Hyundai or Volkswagen care (after long waits). An alternative system is herewith proposed: Proliferate the Public Health Hospital System, which served well on Indian populations and mariners for many years. These public health hospitals could pick up the 15% or less of our population now having problems getting adequate medical attention. These hospitals would also serve the communities well as AIDS hospitals, trauma care centers, and high-risk obstetrics centers. Funding could be 25% by the states and 75% by the federal government. A national value added tax on most luxury items (jewels, automobiles, television sets, etc.) could be used to finance the new public health system.

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1. Waitzkin H: Why it's time for a national health program in the United States. West J Med 1989 Jan; 150:101-107

* * *

To the Editor: The article in the January issue entitled "Why It's Time for a National Health Program in the United States" was most interesting.[1] I am a volunteer attending physician in the Allergy and Immunology Clinic at the University of California, Irvine. In this capacity I am exposed to the same group of patients who have inspired Dr Waitzkin to conclude that we need a national health program.

Most of the patients that I see are refugees from Central and South America and from Southeast Asia. They have risked life and limb to get to this country in search of freedom. I suspect that they would not choose to go home even if their homeland offered a national health program.

The common denominator of the countries that these people are fleeing is "a precapitalistic mercantilism in which a small elite controls a legal system designed to reinforce the privileges of that elite." The preceding quote is from an article in *Forbes*, January 23, 1989, p 80. This article, "The Right Path," reviews a book by Hernando DeSoto entitled *The Other Path.* Mr DeSoto's prescription for the ills of these countries is *less* government involvement in its citizens' lives. Dr Waitzkin's prescription would take us down the same path that has led to disaster in most of the rest of the world.

I agree with Dr Waitzkin that something must be done to help people who cannot afford basic medical care in this country. I have two proposals to that end.

I propose that the "good samaritan" laws be expanded so that any physician or institution providing free care be held immune from legal liability. Most physicians would be willing to provide a certain amount of free care if not for the legal liability that comes with it. I suspect that the poor would find this solution acceptable. Lawyers and politicians would not.

I would also suggest that if immunity from malpractice were not enough to encourage physicians and institutions to care for the impoverished, then reimbursement should be made by tax credits rather than by cash. Administering such a program would consume less government revenue than the huge bureaucracy that would be required by a national health program.

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1. Waitzkin H: Why it's time for a national health program in the United States. West J Med 1989 Jan; 150:101-107

* * *

To the Editor: My compliments to Dr Waitzkin for his commentary, "Why It's Time for a National Health Program in the United States," in the January issue.[1] It seems incredible to me that a country such as ours has been unable or unwilling to establish a functional health program to date. The medical profession must accept a large share of the responsibility for this situation. We have consistently focused on our personal agenda at the expense of a proper leadership role. From the early 1900s organized medicine has opposed federal and state sponsorship of health insurance plans, including funding of maternal and child care programs, because of perceived threats to the prerogatives of the individual practitioner.[2]

It is difficult to say that we have accepted the principle of universal entitlement to basic health care. Issues such as patient dumping and anti-dumping laws certainly argue against it. In my personal practice of emergency medicine, I see patients frequently who cannot be guaranteed proper follow-up by the private or public sector because of financial constraints and overburdened public facilities.

It is time for us, as a profession, to subordinate our special interests and accept the responsibility for developing a uniform national policy consistent with the best interests of patient care in a society with finite resources.

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* * *

To the Editor: The article by Dr Howard Waitzkin in the January issue[1] is both fascinating and informative.

He has not interviewed any Canadian physicians lately or he would know that in Ontario the nurses are about to strike, and the physicians are soon to strike for the second time in four years.

In British Columbia the hospital staff is closed—no new surgeon or cardiologist unless someone dies or moves away. A physician's billing number identifies the location of the

practice and restricts him or her to that area, and a physician cannot move to another area to practice.

As I give more service for discounted fees and slowly slide backwards financially, I am envious of physicians such as Professor Waitzkin, with salary and the luxury of a sabbatical year off.

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1. Waitzkin H: Why it's time for a national health program in the United States. West J Med 1989 Jan; 150:101-107

Newborn Circumcision

To THE EDITOR: This letter is in response to the epitome entitled "Circumcision Revisited" in the February issue.[1]

To be charitable, the piece is inadequate. There is an overwhelming body of literature proving the importance of newborn circumcision as a health measure.

The relationship of all sexually transmitted disease, squamous cell carcinoma of the penis, and human immunodeficiency virus (HIV) infections has been documented as occurring in men with foreskins much more frequently than in those who are circumcised.

I note that the references accompanying the piece are dated from 1985. I would suggest the authors survey the recent literature with a computer search. They will find ample proof of the importance of newborn circumcision as a public health measure that organized medicine should support.

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Pediatric Crohn's Disease

To THE EDITOR: Drs Thomas and Sinatra provided an interesting bit of information in "Screening Laboratory Tests for Crohn's Disease" in the February issue.[1] Their observation that 21 of 24 pediatric Crohn's patients had positive assays for fecal α-antitrypsin (FA) was of particular interest.

I was surprised, however, that the following statement escaped your editorial scrutiny: "Our results suggest that pediatric patients without anemia, abnormal FA excretion, hypoalbuminemia, bloody stools, or an increased erythrocyte sedimentation rate are unlikely to have active Crohn's disease." Although the clinical axiom might be valid, the authors offered no data related to patients without active Crohn's disease, and their results, therefore, cannot suggest anything about this patient group.

The problem relates to the all too frequent confusion regarding the sensitivity and specificity of screening tests. Those who suggest "more widespread" use of such tests—and their editors—should be held to a higher scientific standard.

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1. Thomas DW, Sinatra FR: Screening laboratory tests for Crohn's disease. West J Med 1989; 150:163-164

Professional Integrity

To THE EDITOR: I was very pleased to read your editorial, "Integrity in Medicine," in the February issue.[1] I listened to Bob Petersdorf's litany of medical student, resident, investigator, and practitioner misconduct—a damning aggregation of regrettable professional behavior.[2] I lament that we live in such times.

You editorial's suggestion that professional integrity be made a requirement for membership in organized medicine adds to Bob's message. The American Board of Internal Medicine has felt this way for some time and as you know, insists on the verification of integrity in resident-applicants for certification. The Board must necessarily rely upon observations made locally over time and faces reluctance to record negative comments, fear of litigation, and sometimes a sense of futility among teaching faculties. Humanistic qualities, including the personal commitment to be honest and trustworthy in evaluating and demonstrating one's own skills and abilities, will also be required in the recertification process. With greater competition, new protection for nonmalicious whistle-blowing, and improving professional accountability, recertification may add to your "powerful counterforce."

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Medical Student Writing Award Winner

Chronic Fatigue Syndrome
A Critical Appraisal of the Role of Epstein-Barr Virus

DENISE KOO, *San Francisco*

This paper was chosen from several submitted in response to THE WESTERN JOURNAL OF MEDICINE's 1989 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West.

MALCOLM S. M. WATTS, MD
Editor

The symptom complex currently designated the chronic fatigue syndrome was previously termed the chronic or chronic active Epstein-Barr virus syndrome or the chronic mononucleosis syndrome, prematurely assuming an etiologic role for the Epstein-Barr virus (EBV). This presumption derived from the fact that some patients with the chronic fatigue syndrome have very high or very low titers of certain antibodies to EBV. A review of seroepidemiologic patterns of response to EBV and of studies of patients with the chronic fatigue syndrome shows that these antibody titers overlap considerably both with those of controls or other healthy persons and with those of patients with other illnesses. Given the high prevalence of exposure to EBV, it would be difficult to determine whether the virus caused the syndrome or whether the antibody elevations resulted from the illness, even if distinct differences in titers existed. Other methodologic issues of control selection, laboratory test comparability, and differing case definitions pose problems in studying this syndrome. The recently published working case definition should facilitate the continuing search for causes.

(Koo D: Chronic fatigue syndrome—A critical appraisal of the role of Epstein-Barr virus. West J Med 1989 May; 150:590-596)

The chronic fatigue syndrome encompasses a myriad of definitions that include many nonspecific symptoms. Persistent disabling fatigue lasting at least 1 to 18 months prevails as a constant feature of all definitions. Variably incorporated into the syndrome are fever, pharyngitis, myalgias, arthralgias, headaches, paresthesias, lymphadenopathy, and psychologic or neurologic complaints. Similar syndromes in the past include Iceland disease, epidemic neuromyasthenia, encephalomyelitis, and the postviral syndrome.[1-5] As yet the causes of these syndromes remain unknown.

The resemblance of the chronic fatigue syndrome to a chronic or recurrent form of infectious mononucleosis has provoked investigation of a possible link between the syndrome and the Epstein-Barr virus (EBV), the etiologic agent of infectious mononucleosis. Early studies found presumptive evidence in some patients of persistent EBV infection, as shown by high titers of immunoglobulin (Ig) G antibodies to Epstein-Barr viral capsid or early antigens or a lack of the expected antibodies to EBV-determined nuclear antigens.[6-9] On this basis, despite the fact that healthy persons may have similar titers, some investigators termed the syndrome the chronic mononucleosis syndrome, or the chronic active EBV syndrome, implying that EBV is the cause. To demonstrate the problems with this assumption, I will review briefly the seroepidemiology of the Epstein-Barr virus.

Seroepidemiology of Epstein-Barr Virus

Determining the pattern of antibody response both during acute disease and many years later is necessary to evaluate a possible causative role for EBV in the chronic fatigue syndrome. Comparing the types of antibodies prevalent in both the healthy and the ill—including those with the chronic fatigue syndrome and patients with cancer, immunosuppression, and other diseases—will clarify this issue further.

Based on studies of acute infectious mononucleosis, it is generally thought that during primary infection with the Epstein-Barr virus, IgM against the viral capsid antigen (VCA) and antibody to the early antigens—especially those distributed diffusely throughout the nucleus and cytoplasm, early antigen (EA)-D—appear early, rise in titer, and then decline to undetectable levels, the IgM to VCA after a few weeks, the anti-EA antibodies after a few months.[10-13] The presence of IgG to VCA and antibody against the Epstein-Barr nuclear antigen (EBNA) persists indefinitely,[10,13] although anti-EBNA usually does not develop until several weeks or months after the acute illness.[11] The prevalence of IgG anti-VCA depends on the age and the socioeconomic status of the group sampled, increasing with increasing age and with decreasing socioeconomic status[14-17]; approximately 90% of adults in the United States show serologic evidence of a previous EBV infection. Many questions remain to be answered, however. For example, how long does each type of

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
EA = early antigen
EBNA = Epstein-Barr [virus] nuclear antigen
EBV = Epstein-Barr virus
Ig = immunoglobulin
VCA = viral capsid antigen

antibody persist? Are there variations in the level of antibodies and in antibody response patterns, and, if so, do certain patterns signify "healthier" responses? What composes the range of normal antibody responses?

Several studies of healthy people have attempted to answer these questions. In a prospective study, Niederman and co-workers found EBV antibody at levels of 1:40 or more at least four years after an episode of infectious mononucleosis and up to seven years after asymptomatic seroconversion.[17] Horwitz and associates observed 88 patients for 10 to 104 months after EBV antibody-confirmed infectious mononucleosis.[18] Titers of IgG to VCA remained high (≥1:320) in 56% at 10 to 14 months and in 27% at 40 to 104 months. Anti-EBNA antibody titers ranged from 1:5 to 1:160. In a systematic sample of a semirural community, Sumaya and colleagues found that 98.6% of healthy adults between 31 and 50 years of age had anti-VCA antibody titers of 1:10 or greater[16]; 21% of this age group had titers of 1:160 or greater, and 34% of those older than 50 years had titers as high. Additionally, 100% of healthy pregnant women in two studies showed seropositivity for anti-VCA antibody, with geometric mean titers of 346 and 273, and 95% to 100% were anti-EBNA positive, with geometric mean titers of 43 and 30.[19,20] These studies show the wide range of anti-VCA and anti-EBNA antibody levels found and the duration of their persistence in healthy people.

Because anti-EA is thought essentially to disappear soon after infection, the presence of antibody to the early antigens suggests a recent primary infection, and the presence of IgM to VCA would confirm this fact. Seropositivity instead for anti-EBNA provides evidence for a previous EBV infection. Between 12% and 63% of the patients in the above studies had antibodies to the early antigens, however, with titers of 1:10 or greater, and in another study by Sumaya, 19 of 20 healthy adults tested positive for IgM anti-VCA, anti-EA, and anti-EBNA.[21] The simultaneous presence of all three antibodies may rarely occur after a primary infection,[11] but one would not expect so many persons older than 30 years to have had a recent primary infection. Sumaya suggested that this pattern could be a manifestation of a heterologous antibody response to another virus, but he concluded that it most likely represents a host immune response to an endogenous reactivation of EBV. Given, however, that the persons tested were all healthy and had no history of a mononucleosis-like disease, a definitive conclusion cannot be reached.

Distinct antibody patterns with very high titers of antibodies are commonly observed in EBV-related diseases such as Burkitt's lymphoma and nasopharyngeal carcinoma. African patients with Burkitt's lymphoma have extremely high titers of anti-VCA (87% ≥1:160, geometric mean titer 376), with a variable presence and titers of anti-EBNA; most of them have titers of antibodies to EA—in the restricted cytoplasmic, perinuclear distribution, EA-R—that are significantly higher than in normal controls.[22] A decrease in the titer of anti-EA-R antibodies during remission is predictive of five-year survival. In patients with nasopharyngeal carcinoma, high levels of anti-VCA (86% ≥1:160, geometric mean titer 350) and anti-EA-D antibodies predominate. The presence of IgA to VCA or EA-D is also useful as both a diagnostic and a prognostic tool in cases of nasopharyngeal carcinoma, with titers increasing with higher stages of the disease and decreasing after successful therapy.[22,23]

Interestingly, high titers of anti-VCA antibody also prevail in immunosuppressed patients with malignant or nonmalignant diseases, such as lymphoproliferative disorders or other cancers, sarcoidosis, systemic lupus erythematosus, and immunodeficiency diseases. The antibody titers in these diseases generally do not rise as high as those in patients with Burkitt's lymphoma, nasopharyngeal carcinoma, or infectious mononucleosis. Of 489 patients with Hodgkin's disease, 40% had titers of 1:160 or greater, with a geometric mean titer of 105, and of 235 patients with chronic lymphocytic leukemia, 45% had titers of 1:160 or greater with a geometric mean titer of 110.[22] These patients may also have IgM anti-VCA and low, absent, or normal levels of anti-EBNA.[24] In addition, renal transplant patients often have high levels of anti-VCA, low levels of anti-EA-R, and no anti-EBNA antibody.[23] Thus, serologic evidence of "abnormal" or "reactivated" EBV does not necessarily confirm the presence of disease caused by EBV, for immunosuppressed patients have no illness presumed to be caused by Epstein-Barr virus.

In summary, antibody responses to Epstein-Barr virus show many serologic patterns. Any or all of the EBV antibodies discussed have been found in healthy persons long after a primary infection. Pregnant women, hospital inpatients, and immunosuppressed patients also have a high prevalence of anti-VCA, anti-EA, and anti-EBNA antibodies without apparent clinical evidence of EBV-related disease. Moreover, while the levels of these antibodies generally do not surpass those found in persons with known EBV-related diseases, the high titers exceed those traditionally expected many years after an EBV infection. Reviewing these seroepidemiologic patterns of response to EBV enables a critical evaluation of the etiologic hypothesis relating EBV to the chronic fatigue syndrome.

Chronic Fatigue Syndrome

The term "chronic fatigue syndrome" is vague. This symptom complex comprises fatigue or easy fatigability, malaise, and sometimes pharyngitis, fever, or other symptoms, but it has few signs and no proven cause. Because it often follows a flulike illness and resembles a chronic form of mononucleosis, the syndrome has been more specifically termed the chronic Epstein-Barr virus syndrome, chronic active EBV infection, or the chronic mononucleosis syndrome. The lack of specificity, however, of either the syndrome definition or the symptoms themselves warrants withholding such terminology, especially as the evidence linking EBV to the syndrome is tenuous at best. Despite the problematic definition, investigators currently prefer to use the term chronic fatigue syndrome because it describes the most salient clinical feature of the syndrome and does not imply a particular cause or causes.[25]

The more specific terms usually label syndromes more clearly associated with EBV. Chronic active EBV infection often is used for patients with underlying primary or sec-

ondary immunodeficiency states who have extremely high titers of anti-VCA and anti-EA antibodies and absent or lower titers of anti-EBNA. These patients have extensive disease caused by polyclonal B-cell lymphomas that are positive for the EBV genome or EBNA.[26,27] Recently Jones and co-workers described three patients with chronic recurring disease and objective signs such as hepatosplenomegaly, pancytopenia, weight loss, and extraordinarily high titers of anti-VCA (1:10,000) and anti-EA-D (1:640) and low or normal titers of anti-EBNA.[28] On postmortem examinations they discovered polymorphic T-cell lymphomas positive for the EBV genome. Chronic EBV syndrome also refers to a severe disease with high titers of EBV antibodies (with either high or absent anti-EBNA) and clinical signs such as fever, pneumonitis, and lymphoid hyperplasia and polyclonal hypergammaglobulinemia[29] or pancytopenia,[30] a syndrome unlike the chronic fatigue syndrome.

Descriptive Epidemiology

As reported in recent literature, persons suffering from the chronic fatigue syndrome are mostly white and of a higher socioeconomic status, with twice as many women afflicted as men.[6-9,31] They range in age from 3 to 56 years, with a mean age of approximately 30. Dubois and associates noted no blacks among his patients with the chronic fatigue syndrome, even though blacks constitute half of Dubois's private practice.[7] Of 14 patients in the Dubois study, 9 had college degrees, as did 21 of 23 patients in the study of Straus and colleagues.[7,9]

Many aspects of the chronic fatigue syndrome limit our acceptance of this admittedly sketchy descriptive epidemiology. Because each investigator had his or her own slightly different definition of the syndrome, we cannot be certain that each group of patients has the same disease. In fact, due to the nonspecific case definition, we do not even know that the patients within each study have the same disease with the same cause.

Because these patients were often drawn from physicians' private practices,[9,31] they may not represent well members of the general population with this syndrome. Media publicity may have led some patients to their physicians. Referral bias probably played a role once certain investigators communicated a special interest in the syndrome.[7,9,31] It may be asked whether those of higher socioeconomic classes are more susceptible to this problem or whether they merely have better access to physicians, particularly these physicians, than the poor.

More important, the inclusion by some investigators of "abnormal" EBV findings on serologic tests—IgM anti-VCA, anti-EA, and high IgG titers of anti-VCA[6-8]—in the case definition further limits the representativeness of the patients studied. The ubiquitous prevalence of EBV infection in serologic examinations in the United States population makes it difficult to sort out true and false linkages; including EBV serologic study in the case criteria overestimates EBV linkage with the chronic fatigue syndrome.

Etiologic Studies

Many studies have attempted to confirm the role of EBV in the chronic fatigue syndrome. They have investigated patients with some of the various symptoms, evaluating their EBV antibody status and titers and comparing the percent of positive antibody titers with those expected in normals or found in control populations. Some studies have noted significant differences in antibody status or titers between cases and controls. These values have little diagnostic value not only because the controls are often poorly chosen or ill-defined, but also because the results overlap with both those of the healthy controls and those expected in patients with other illnesses. A lack of uniformity in case definitions and in laboratory standards, the latter both within and between studies, may also blur true distinctions or create artificial differences. A major problem with these studies, even if distinct differences existed, is that they are essentially prevalence studies; therefore, whether EBV caused the fatigue syndrome or the antibody elevations resulted from immunologic activation due to the illness would be difficult to determine.

One of the earlier studies by Tobi and co-workers sought EBV-definitive serologic findings in a case series.[6] In their patient population "derived from a large group . . . in which a viral etiology was suspected," they selected seven who had symptoms for more than a year, no other serious disease, and the presence of IgM anti-VCA for that year. These patients tested negative for rheumatoid factor, which can cause a false-positive test result for IgM anti-VCA. In this group of patients, the authors also found high titers of IgG anti-VCA ($\geq$ 1:128) and titers of anti-EBNA antibody persistently 1:40 or higher. Four of the seven also tested positive for anti-EA-R ($\geq$ 1:8). The coincidence of IgM anti-VCA with anti-EBNA is unusual because these antibodies signify distinct temporal relations to primary infection,[13] although as mentioned above such a combination has occurred in asymptomatic persons.[21] Tobi and associates thought that this serologic pattern may indicate a reactivation of EBV, but the selection of only IgM-positive cases and of no IgM-negative cases or IgM-positive controls for comparison makes it difficult to draw any conclusions regarding a causal role for EBV.

Dubois and colleagues studied 14 patients largely from Dubois's private practice in Georgia.[7] These patients were chosen on the basis of chronic fatigue and malaise in association with "serologic findings of active EBV infection." For serologic studies, the investigators used three different laboratories and did not specify which laboratories did which tests, nor did they mention whether the laboratories had comparable results. They used controls largely for reference values, picking 19 female and 12 male hospital personnel, neither age- nor sex-matched to cases. All cases tested positive for IgG to VCA (range of multiple specimens from cases, 1:40 to $\geq$ 1:1,280), anti-EA, and anti-EBNA, and negative for IgM to VCA. By comparison, none of the controls tested positive for anti-EA, and their titers of IgG generally fell in a lower range (1:40 to 1:320), although they were not compared directly and the actual values are not given. In two patients, anti-EA titers disappeared although the patients remained symptomatic, while another patient continued to have an anti-EA titer but became asymptomatic. Despite the fact that they chose the patients based on their unspecified "serologic evidence of active EBV infection" (perhaps excluding those who were anti-EA-negative), and the fact that anti-EA titers were not fully predictive of symptoms, the authors concluded that "anti-EA is a key serologic marker for CMS (chronic mononucleosis syndrome)."[7]

These patients also differed from the general population, however, in factors for which the investigators did not select. In 12 of 14 patients, cytomegalovirus (CMV) antibody titers

were significantly higher than those of a group of randomly selected blood donors ($P < .001$). Although different laboratories evaluated the CMV antibody titers, the authors noted that at least five patients had evidence of active CMV infection. They also found variable, mild immunoglobulin deficiencies (no numbers given) in 10/14 cases, and in 6 of 7 tested they found slightly decreased T4/T8 ratios—less than one standard deviation below normal. These data could just as easily provide evidence for a cause or for a result of EBV "reactivation."

Jones and co-workers reported on a year-long follow-up of 44 patients aged 3 to 54 referred for evaluation of persistent or recurrent illnesses, with symptoms that included but did not require fatigue, lymphadenopathy, fever, and headaches.[8] Their definition of illness and their inclusion of 18 (41%) children raise the issue of comparability with other studies. Only 39 of these patients tested positive for the EBV antibody, with all 39 positive for IgG anti-VCA and anti-EA. Of 33 age-matched healthy controls from a source or sources not described, 30 tested positive for IgG anti-VCA, but only 3 of the 30 tested anti-EA-positive. Case anti-VCA and anti-EA titers were significantly higher than the respective titers of the controls ($P < .001$). In the graphic representation, however, the ranges of case and control titers overlapped substantially. Jones and colleagues noted a "recognizable" pattern of anti-EA elevation with a recurrence of symptoms in 89% of the patients, but they acknowledged both the presence of anti-EA in healthy persons, including 10% of their seropositive controls, and the possibility that elevated anti-EA levels may follow rather than precede the underlying problem, as a marker of secondary viral "reactivation."

Physicians at the National Institutes of Health and in 11 states referred 31 patients to Straus and associates for their appraisal.[9] These patients gave a history of chronic illness with fatigue lasting at least a year after infectious mononucleosis or a mononucleosis-like disease, and their physicians had declared themselves unable to explain the illnesses. In their article, Straus and co-workers focused on the 23 EBV-seropositive persons. It is important to note that diagnoses initially missed by the patients' primary physicians were finally made in five of the eight seronegative patients. The diagnoses were, respectively, Sjögren's syndrome, systemic lupus erythematosus, poorly differentiated nodular lymphoma, transverse myelitis and Hodgkin's disease, and multiple sclerosis.

They compared the antibody status and titers of the 23 patients with those of 23 age- and sex-matched seropositive controls. As in the article by Jones and associates, the source of the controls was not described. With the use of the highest reciprocal values of those titers drawn from the cases, the geometric mean titer of case IgG anti-VCA was significantly higher than that of the controls (518 versus 71, $P < .001$). These comparisons were problematic, however, because they compared multiple specimens from cases with single specimens taken from controls; 19 of 23 cases had at least some values in the reference range given for "normal seropositives" and 9 of 23 had all values fully within this range. Two different laboratories did the serologic testing; no report is made of their comparability or reproducibility. Other antibody results, with similar methodologic errors, include 19/23 anti-EA-positive cases versus 6/23 anti-EA-positive controls, 16/23 anti-EBNA-positive cases versus 23/23 controls, and 5/23 cases intermittently positive for IgM anti-VCA versus 0 controls. Straus and co-workers discovered that one IgM-positive result was falsely caused by a rheumatoid factor, but the other four results were not reevaluated.[9]

On the basis of the foregoing evidence, Straus and colleagues discussed the possibility of a causal role for EBV in the fatigue syndrome.[9] They cited the following as support: some of the illnesses began with acute infectious mononucleosis; virus-specific antibody levels were elevated, while antibody levels to *Toxoplasma gondii*, CMV, and other viruses were not; and the increased T cell-mediated suppression of immunoglobulin synthesis by EBV- or mitogen-stimulated B cells resembles T-cell activity seen in acute infectious mononucleosis.[32] Although many of the patients' illnesses began with mononucleosis, manifesting a primary EBV infection as infectious mononucleosis could initiate or merely indicate an immune system at risk for superinfection or other disease. As they selected these patients based on their EBV antibody status and many of the titers are within normal range (in addition to overlapping with those of the controls), the antibody results constitute scant evidence for EBV as a cause of the patients' illnesses. Straus and co-workers also pointed out that 7/23 patients lacked anti-EBNA, a defect that has been observed in the immune-deficient persons.[23,24] Together with the suppressor T-cell activity, such data suggest immune dysfunction but give no proof of cause.

Both Miller and colleagues and Henle and associates searched specifically for chronic EBV markers, reporting complementary, equally inconclusive results.[33,34] In patients diagnosed with "chronic active EBV," both groups assessed antibody responses to specific EBNA components. Miller and co-workers discovered that 4 of 39 (~10%) patients lacked anti-EBNA-1 antibodies.[33] Pointing out that 100% of 33 healthy adults, 30 nasopharyngeal cancer patients, and 18 cancer patients have anti-EBNA-1 antibodies, they said that a lack of anti-EBNA-1 may serve as a selective marker for the chronic fatigue syndrome. The lack of sensitivity of such a marker is augmented by a lack of specificity: 80% (12/15) of children with the acquired immunodeficiency syndrome (AIDS) in their study and 10% (4/43) of those with Burkitt's lymphoma also lacked the antibody.

Based on the premise that after infectious mononucleosis, anti-EBNA-2 antibody levels first rise and are later eclipsed by anti-EBNA-1 antibodies, Henle and colleagues measured and compared the levels of these antibodies in healthy and in ill persons. Of 38 healthy seropositive controls, all positive for anti-EBNA-1 antibodies, all had the expected anti-EBNA-1 levels that were greater than anti-EBNA-2 levels. Only 28% (20/70) of patients with the chronic fatigue syndrome had the "abnormal" result, with anti-EBNA-2 levels greater than anti-EBNA-1 levels. In addition to these indeterminate results, the authors remarked that patients with Hodgkin's disease, non-Hodgkin's lymphoma, AIDS, and other immunodeficiency diseases often have similar reversed ratios.

Two studies more rigorously examining this problem were published back to back in 1987. Both Holmes and associates and Buchwald and co-workers carefully delineate the origin and comparability of their study patient populations with their pools of patients, in addition to detailing more completely their methods.[31,35]

Holmes and colleagues interviewed by phone 134 of 139 patients who had been tested serologically for EBV in Nevada. These patients, suffering from fatigue, originated from

an office practice set in the well-to-do resort community of Incline Village. Attempting to make the type of illness studied as uniform as possible, they defined case-patients as those with "persistently increased fatigue lasting at least one month . . . sufficient to cause absence from work for two weeks or longer or reduction of daily activity by 50% or more, with no apparent explanation." Only 15 patients fit this definition; of the rest, "non-case patients," 101 had fatigue that resolved in less than a month or was not as severe and 18 had other possible reasons for fatigue. They compared serologic values of the cases with those of both non-case-patients and 30 age-, sex-, and race-matched controls with no history of fatigue or of EBV testing, 21 of whom were patients from the office practice scheduled for routine laboratory tests, the other 9 being office staff.

They evaluated the antibody data both for potential threshold titers and for differences between geometric mean titers. Generally antibody titers of cases fell above those of either non-case-patients or controls. Significant differences existed at some thresholds and between certain geometric mean titers, but no antibody values could be used to distinguish cases from either of the other two groups because much overlap existed between the groups of values. Among cases and controls, they also compared titers of antibodies to CMV, herpes simplex virus types 1 and 2, and measles, finding that cases tended to show values above those of controls for the other viruses also.

Holmes and co-workers concluded that EBV serologic findings are inadequate for diagnosing the chronic fatigue syndrome and that the evidence is inconclusive regarding an etiologic role for EBV.[31] Having compared the variability of EBV serologic test results both within and between three laboratories, they also decried the subjectivity and the lack of reliability of the test results, a significant point for future studies and for interpreting previous studies. They pointed in addition to the necessity of remaining open to other possible causes of these illnesses.

Buchwald and associates approached the etiologic question from a different angle.[35] Rather than study highly selected patients with the chronic fatigue syndrome, they conducted a prospective study to ascertain the prevalence of the syndrome in a general practice setting and to determine the usefulness of EBV antibody testing in such patients. During a six-month period, they interviewed 500 patients coming to the practice for any reason. Their general patient population was not described, although these 500 were said to be representative of all patients between the ages of 17 and 50 years seen in the practice during this period. Included as cases were patients having both severe loss of energy or easy fatigability for more than six months and either pharyngitis, myalgias, or headaches. Pregnant women and patients receiving steroids or with certain chronic diseases were excluded. Of 103 who fit the case definition, only 40 patients consented to participate in the study. Superficially the investigators found no participation bias, as the nonparticipants did not differ significantly in age, sex, or severity of symptoms.

Buchwald and co-workers chose 40 age- and sex-matched controls from those patients scheduled for routine blood tests.[35] A technician unaware of case or control status tested pairs of specimens for EBV antibodies in parallel. No significant differences were found in comparing cases with controls for the presence of VCA-IgG, anti-EA, anti-EBNA, and IgM anti-VCA, nor for certain threshold titers of these antibodies. The geometric mean titers of cases were not significantly higher than those of controls, although the patients had been divided by certain symptoms into five overlapping groups, decreasing the ability to detect a difference in these smaller-sized cells.

Buchwald and colleagues recognized that their patients, who were not seeking care primarily for their fatigue, perhaps could not be compared with the sick or disabled patients in previous studies.[35] They noted that their patients generally had lower antibody levels, and they also acknowledged the flaws in comparing results from different laboratories. As to the relevance of the investigation of the chronic fatigue syndrome, their patients' fatigue and related symptoms, while perhaps not as severe as others had reported, had caused considerable morbidity for a median duration of 16 months. These authors also cited as their rationale the need for studies more representative of the syndrome as manifested in the general population, not merely in groups of highly selected patients. In their patient population, Buchwald and co-workers found no predictive value in EBV serologic testing and no evidence for a causal role for EBV.[35]

Methodologic Issues

The evaluation of the chronic fatigue syndrome and the possible etiologic role of EBV brings with it methodologic problems. Some of these matters arise from investigators' choices of methods, while others are inherent to the study of this disease.

In fact, whether the syndrome comprises only one disease or many diseases with diverse causes is uncertain. The various overlapping, nonspecific case definitions may represent either a spectrum of one disease or distinct diseases that are difficult to separate clinically, and the lack of a strict case definition undermines the ability of studies, both individually and as a whole, to find any one cause. Therefore, while recognizing that the syndrome may not necessarily comprise a single disease, several investigators have published a working case definition to facilitate further research and to increase the comparability between future etiologic studies.[25]

The case finding in these studies requires that the representativeness of these patients—mostly higher socioeconomic class and EBV antibody-positive—be examined. Many of these patients come from selected, highly referred physicians' practices. Other patients may remain undiagnosed because their physician has not heard of or does not believe in the existence of the syndrome. Other patients with the chronic fatigue syndrome may have little access to the media or to physicians. In addition, the inclusion of EBV-antibody positivity in some case definitions automatically excludes those patients with symptoms but without EBV antibody on serologic tests. The proper methods should involve an evaluation of these latter patients, for selecting the cases by the factor to be assessed invariably will overstate the linkage of EBV with the syndrome. Henle and associates noted that they have data, as yet unpublished, regarding a group of patients with symptoms of the chronic fatigue syndrome but no EBV antibodies.[34]

The choice of controls in these studies raises another methodologic issue. Tobi and colleagues had no controls,[6] while other investigations had poorly matched or incompletely described controls.[7-9] Although in later studies con-

trols were selected more carefully than in the earlier ones,[31,35] these controls still were mostly healthy patients having routine laboratory tests. Perhaps sick patients, with illnesses unrelated to EBV, would serve better as controls, for the chronic illness in patients with the chronic fatigue syndrome might be expected to manifest with immunologic aberrations such as a "reactivation" of EBV or other antibodies; using ill persons as controls would permit a recognition that such an event could occur secondary to other prolonged illnesses. As noted earlier,[13,22] hospital inpatients with illnesses presumed to be unrelated to EBV often have some elevated EBV antibody levels.

Laboratory test comparability becomes an issue in studies that rely heavily on EBV serologic test results. It is difficult to compare results when the studies encompass various definitions of what is a positive outcome—for instance, an anti-EBNA titer of 1:8[13] or 1:40.[6] Even if the same threshold titers are used, the results could not be compared, for no laboratory standards exist. Subjective end points for the tests, the varying quality of reagents used, and disparate technicians' abilities in the different laboratories detract from the reliability and validity of serologic results within and between studies. Laboratory standardization clearly is needed.

Even if these studies had shown a more consistent association of certain EBV antibody titers with the chronic fatigue syndrome, they are essentially prevalence studies, and therefore cause and effect cannot be differentiated. As noted earlier, EBV infection and the presence of EBV antibodies are common; EBV seropositivity alone does not indicate an etiologic role. High titers of antibodies might signify confounding factors and not causality, as such high titers could result from a nonspecific immune activation due to the illness. Persons with illnesses unrelated to EBV and even healthy persons have had equally high titers.

Conclusion

These etiologic studies have found generally higher prevalences or levels of EBV antibodies in patients with the chronic fatigue syndrome than in healthy controls but without any clear distinctions between patients and controls. The patients' antibody titers at times matched those of the controls. Often they fell above or below control values in a given study, but still within the range found for healthy normal persons in studies of EBV serologic patterns.[13,15,16] These prevalences and titers also did not exceed those seen in conditions unrelated to EBV, such as pregnancy, cancers, and immunosuppression. The lack of predictive value for individual serologic patterns emphasizes the lack of specificity of EBV serologic findings for the chronic fatigue syndrome, a conclusion corresponding to that of Holmes, Straus, and others.[25,31,35-37]

In their attempts to find other markers for the syndrome, several studies found nonspecific immunologic dysfunctions in patients with the chronic fatigue syndrome,[7,9,38] evidence for the existence of disease but not for its cause or effect. The presence of antibody to other viruses in the studies by Dubois and Holmes and colleagues[7,31] and the fourfold rise in titers to EBV among seven patients with other viral or tuberculous illnesses in the Tischendorf study[15] raise the question of polyclonal B-cell activation or anamnestic antibody responses. A study of the "postviral fatigue syndrome" noted also a syndrome resembling the chronic fatigue syndrome, with vague immunologic dysfunction, but with a significant prevalence of antibody only to Coxsackie B viruses.[5] Perhaps different viruses are causing a similar syndrome.

The foregoing studies, with their methodologic problems, have found no etiologic role for EBV in the chronic fatigue syndrome, although they did not rule out the possibility that EBV causes some cases of the fatigue syndrome. Straus has suggested that some patients, in particular those with the most "severe" serologic abnormalities and an illness developing after proven infectious mononucleosis, may have a chronic EBV infection.[39] Because exposure to and infection with the virus is so common, however, more informative studies regarding its etiologic role in the syndrome must await further advances in the science of the Epstein-Barr virus. A more complete understanding is needed of the pathophysiology of the events after primary infection, the mechanism of latency and reactivation, and the functions of specific parts of the EBV genome. Whether certain EBV strains could be lytic rather than latent is still unknown. With such knowledge, we might understand whether EBV antibody elevations signify primary or secondary viral reactivation and contribute to morbidity, or whether such elevations are merely an epiphenomenon.

Because of the relative lack of objective findings, some physicians dismiss the chronic fatigue syndrome as a psychoneurotic manifestation. Komaroff argues for an organic basis for this disease or diseases, citing the following reasons: patients have symptoms not seen in other psychoneuroses; some patients have laboratory test abnormalities (other than EBV serology); patients all give the same history of good health abruptly altered by this syndrome; and, the reported occurrence of clusters of disease suggests an infectious or environmental agent.[36] Straus supports the view of an organic cause, noting that the syndrome may represent a "general response to various psychological or physical irritants."[37] He nevertheless declares the need for more information in the area of psychopathology and the potential interaction between the psyche and the immune system.

Finally, physicians and scientists should not neglect other alternatives. Before treating patients with nonspecific, unproven γ-globulin[40] or acyclovir—recently shown in a placebo-controlled trial to be unhelpful in the syndrome[41]—physicians are well advised to recall those patients excluded from the Straus study with diseases that their primary physician had not discovered.[9] An important feature of the recently published working case definition is the extensive list of known diseases that must be ruled out before diagnosing the chronic fatigue syndrome.[25] For epidemiologists and other scientists, suggestions of possible causes of the syndrome include a new virus—human B-cell lymphotropic virus[42,43]—other viruses, other infectious or environmental agents, and even postviral thyroiditis.[44] One or all may cause the chronic fatigue syndrome, but unfortunately none have yet been investigated. The future should produce studies of these and other possible causes of the syndrome.

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Quality of Care

Physicians Investigated for Inappropriate Prescribing by the Oregon Board of Medical Examiners

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We retrospectively reviewed all allegations of inappropriate prescribing investigated by the Oregon Board of Medical Examiners from 1981 through 1986. Inappropriate prescription writing accounted for 51% of all investigations during this period, with controlled drugs, primarily opiates and benzodiazepines, accounting for most complaints. Of 130 physicians investigated, more than half had previous complaints; 50 were ultimately restricted or disciplined by the board. Inappropriate prescribing of controlled drugs is probably underdetected and frequently repeated. Available literature suggests that inappropriate prescribing of other drugs, especially antibiotics, is extremely common, but such problems were rarely identified by the current discovery and review processes of the Oregon board. Inappropriate prescribing will require increased attention from physician educators and licensing boards.

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Increasing societal and professional demands for regulation have led to more monitoring of professional practices by various regulatory bodies, including local hospital boards and the federal government. State medical licensure boards are gradually assuming a greater role in the regulation process. Some have responded vigorously; others investigate few complaints and discipline few physicians (*Psychiatric News,* January 12, 1987, p 12). The Oregon Board of Medical Examiners (BME) has been at the forefront of disciplinary and rehabilitative activity.[1]

We describe the characteristics of physicians brought before the Oregon board for alleged inappropriate prescribing practices and the system devised by the BME to evaluate and take action on the complaints. To date, reports in the medical literature have focused on the interaction between regulatory and treatment systems and impaired physicians. Reports from Georgia,[2] California,[3] and Oregon[4,5] have highlighted the problems of physicians who suffer from substance abuse, mental illness, or both. None have focused on the response of a board of medical examiners to the problem of inappropriate prescription writing. In Oregon this is the largest single category of complaints lodged against physicians.

Review of the Literature

The prescribing patterns of physicians have been studied sporadically since the 1950s.[6] These studies have shown some of the broad influences on physician prescribing habits, including factors associated with high rates of psychoactive drug prescribing.[6-10] These data suggest that, in general, older physicians in solo practice, with less specialty training, larger practices, and high daily patient volumes are most likely to prescribe drugs, including psychoactives, and tend to continue prescriptions for longer periods of time. Physicians who think that patients expect to receive drugs are also more likely to prescribe them, especially psychoactive drugs.[7] It appears that a small percentage of physicians accounts for a large proportion of inappropriate prescription writing.[8,10] One study reported that 4% of a hospital staff accounted for 50% of inappropriate prescriptions.[8]

Research on factors influencing physician prescribing patterns suggests that there may be differences between physicians identified as having prescribing problems and other physicians. Physicians without identified problems appear to modify their prescribing practices to a moderate extent in response to a variety of interventions, including specific education,[11-13] details about their prescribing practices,[8,14] or the existence of policies restricting the availability or limiting quantities that can be prescribed.[15-17] Psychoactive drug prescribing in general appears to be less amenable to these influences.[10,18] Unfortunately, the prescribing practices of offenders may be the most difficult to change.[8,10]

There is a dearth of data about how patterns of inappropriate prescribing are developed, about how to identify physicians with this problem, and about the course of their problems, their interactions with licensing agencies, and rehabilitation. It is not known if such physicians are in some way impaired; certainly some physicians inappropriately prescribe for themselves.[17]

Methods and Procedures

The Oregon Board of Medical Examiners is composed of eight physicians and one lay member appointed by the governor to four year terms. The board investigates all complaints made against physicians, podiatrists, physician assis-

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tants, acupuncturists, advanced medical emergency technicians, and, at the time of the study, nurse practitioners with prescribing privileges. Our report will focus primarily on physicians.

Complaints to the Oregon BME are initially screened by investigative staff, and those complaints that may constitute possible violations of the Oregon Medical Practice Act[19] are referred to the investigative subcommittee of the BME for further investigation. This committee is composed of four members of the board, including the lay member. A further screening process takes place at this stage; some complaints are closed, while those viewed as serious and substantive are investigated further. At this time the physician is requested to appear for an interview with the investigative committee at its monthly meetings. In addition to the members of the investigative committee, the executive director of the BME, the board's attorney, and a medical and psychiatric consultant are all present at the meetings. The purpose of this interview is to gather more information regarding the complaint, to review the pertinent medical records, and to hear the physician's side of the issue in question. The physician may bring an attorney to the investigative committee meeting. Following the interview the committee can recommend closing the case with or without a letter of concern to the physician. If the question of a potential violation of the Medical Practice Act remains, the case will be referred for review by all nine members of the BME.

Study data were gathered by retrospectively reviewing all complaints of inappropriate prescribing that reached the stage of licensee interview by the investigative committee from 1981 through 1986. Each case was followed until a disposition of the complaint was reached. We chose this stage in the process because these complaints had been deemed serious enough to warrant an interview. We could also identify the characteristics of the physicians interviewed and how the system functioned at both the investigative committee and full board levels. This was also the earliest point in the process where accurate and meaningful data became available.

Data were gathered from three sources. The Oregon BME maintains a computerized file of demographic and educational information on all physicians licensed in Oregon. In addition, we reviewed the board's investigative file for each new complaint of inappropriate prescribing during the study period 1981 through 1986. This review included the type of complaint, who initiated it, the types of drugs involved, and a review of all previous complaints. Finally, we reviewed minutes from meetings of the full board where final actions are recorded. For physicians with multiple complaints during the study period, the first time they appeared before the investigative committee was designated the key complaint. Detailed descriptions of the key complaint, the three most recent complaints before the key complaint was made, and actions taken by the investigative committee and the board as a whole were compiled. A confidential research data file was developed to ensure anonymity.

Results

The Complaints

The Oregon Board of Medical Examiners groups complaints into 13 separate categories. In the six-year study period (1981 through 1986), 300 complaints resulted in informal interviews with the investigative committee of the board. Of the 300 complaints, 154 (51%) were of inappropriate prescription writing. The next most frequent category, complaints of habitual or excessive use of intoxicants, accounted for only 39 (13%) of the total. The number of inappropriate prescribing complaints investigated each year ranged from a low of 18 in 1982 to a high of 31 in 1986. These 154 complaints involved 140 persons, of whom 10 (7%) were not physicians. The rest of this report will focus only on complaints against the 130 physicians.

The origins of complaints against physicians are shown in Table 1. Of the complaints, 40% originated with the board's own investigative staff, who routinely do periodic but nonsystematic reviews of pharmacy records. The investigators review such records statewide, but their activity is concentrated in the Portland metropolitan area. Insurance companies, mainly the State Accident Insurance Fund, medical professionals (mostly physicians and pharmacists), and regulatory agencies such as hospital boards accounted for another 39% of complaints. Patients or their families accounted for only 5% of complaints.

The Drugs

An average of 1.9 drugs was mentioned per complaint. Only 10% of the complaints involved primarily noncontrolled drugs. Table 2 lists, by generic name, the ten drugs most frequently mentioned in the complaints. These drugs are all controlled and together accounted for 60% of all those mentioned. Opiates were most frequently cited, followed by benzodiazepines. Schedule II drugs were noted 109 times (44%) and schedule III drugs 64 times (26%). The almost exclusive identification of controlled drugs in these complaints is a striking finding that will be discussed further.

TABLE 1.—*Origin of Complaints of Inappropriate Prescribing*

Source	Physicians (n=130)* No.	%
Board of medical examiners' pharmacy check	52	40
Insurance company	20	15
Medical personnel	17	13
Regulatory boards	12	9
Patients, families	7	5
Legal agencies	2	2
Other	12	9

*Source could not be determined for 8.

TABLE 2.—*10 Drugs Most Frequently Cited as Inappropriately Prescribed, 1981 Through 1986*

Drug	Class	No. of Times Mentioned	Cases (n=130), %*
Oxycodone	Opiate	34	26
Codeine	Opiate	34	26
Diazepam	Benzodiazepine	17	13
Meperidine	Opiate	14	11
Hydrocodone	Opiate	11	8
Hydromorphone	Opiate	11	8
Propoxyphene	Opiate	10	8
Pentazocine	Opiate	8	6
Dexedrine	Stimulant	6	5
Flurazepam	Benzodiazepine	6	5

*Totals exceed 100% because most complaints involved 2 or more drugs, including drugs from more than 1 class.

The Patients

Most complaints involved specific patients rather than a physician's general prescription writing practices, although many questioned the treatment of more than one patient. Data concerning the nature of a patient's treatment history were available for 133 patients involved in 74 of the 130 investigated cases. Five general classes of patients could be described: pain patients (55%); drug-seeking patients, including those with a suspected history of drug abuse (24%); friends or family members of the physician, including the physician (11%); patients complaining of anxiety or depression or both (6%); and patients seeking medication for obesity or weight reduction (4%). Of the 73 pain patients, 42 (58%) complained of back pain. These types of patients are consistent with the types of drugs most commonly identified in the investigated cases.

The Physicians

The group of 130 physicians studied consisted of 127 men and 3 women; 116 had MD degrees and 14 DO degrees, and 125 were graduates of American medical schools. Table 3 shows the specialties of these physicians. Family practice, general practice, and internal medicine were the only specialties that exceeded 10% of the sample. Most practiced in the Portland area, probably reflecting the concentration of the BME investigators' activities rather than regional differences in behavior.

Physicians' ages and years since medical school graduation are given in Table 4. The mean age was 54, ranging from 32 to 88. The mean number of years since medical school graduation was 26, ranging from 1 to 59. Of the physicians in the study, 38% were within 20 years of medical school graduation.

The BME records allowed a review of complaints investigated before the study period. We coded detailed information on as many as three previous complaints and counted and categorized any additional complaints. Detailed information was available back to 1977; older records had been purged. Of the 130 physicians, 63 (48%) had not been investigated previously. The other 67 physicians had a total of 123 previous complaints investigated since 1977. Of these, 86 (70%) were of inappropriate prescription writing, followed by 8 (7%) for possible substance abuse and 6 (5%) for possible unprofessional conduct.

Board Action

Board action was determined by examining the results of the first (key) complaint of inappropriate prescription writing lodged against subjects during the six-year study period. Of the 130 key complaints, 75 (58%) were terminated at the investigative committee level, while 55 (42%) were reviewed by the entire board. Of the 75 terminated by the investigative committee, 45 (60%) were closed, 12 (16%) were kept open and further monitored by BME investigators, and 19 (24%) were either still pending or had other outcomes, including retirement of the physician. In addition to these actions, 28 physicians (37%) were also sent a letter of concern.

Of 55 cases that reached the full board, 5 (9%) were closed with no further action; 34 physicians (62%) agreed to a voluntary limitation of their right to prescribe controlled substances. Other outcomes for 16 (29%) included being required to take a federal licensing examination, file triplicate prescriptions, probation, license suspension (one physician), and voluntarily surrender license (one).

Physicians whose cases were closed at the investigative committee level did not differ significantly from those whose cases reached full board hearings in type of medical degree, age, years since medical school graduation, or specialty. Of 52 cases referred to the Oregon BME by its own investigators, 26 (50%) were sent on for full board review, while only 13 (25%) of the 51 cases referred from insurance companies, medical personnel, and other regulatory boards were sent for full board review. The cases discovered by the board's own investigators were significantly more likely to be referred on by the investigative committee to the full board ($\chi^2 = 5.6$, degrees of freedom [*df*] = 1, $P < .02$).

Table 5 shows that a greater percentage of physicians whose cases were referred for a full BME review had previous investigations by the board. Of the 55 physicians reviewed by the full board, 35 (64%) had a history of previous investigations, compared with 43% of physicians whose

TABLE 3.—*Specialty of Investigated Physicians*

Specialty	Physicians (n=130) No.	%*
Family practice	39	30
General practice	30	23
Internal medicine	16	12
Orthopedic surgery	9	7
Psychiatry	6	5
General surgery	5	4
Gastroenterology	3	2
Neurology	3	2
Neurologic surgery	3	2
Obstetrics and gynecology	3	2
Otolaryngology	3	2
Cardiology	2	2
Pediatrics	2	2
Anesthesiology	1	1
Emergency medicine	1	1
Endocrinology	1	1
Physical medicine and rehabilitation	1	1
Rheumatology	1	1
Urology	1	1

*Total exceeds 100% due to rounding.

TABLE 4.—*Demographics of Sample*

Age, years	Physicians (n=130) No.	%
32-39	20	15
40-49	33	26
50-59	29	22
60-69	31	24
70-79	16	12
80-88	1	1
Mean=54 years, standard deviation=13.7		
Years Since Medical School Graduation	**No.**	**%**
<10	11	8
10-19	39	30
20-29	32	25
30-39	27	21
40-49	17	13
50-59	4	3
Mean=26, standard deviation=12.8		

TABLE 5.—*Previous Actions Investigated by Board of Medical Examiners*

Number of Past Actions	Full Board Appearance (n=55), No. (%)	No Board Appearance (n=75), No. (%)
0	20 (36)	43 (57)
1-2	19 (35)	24 (32)
3-4	7 (13)	4 (5)
5-6	3 (5)	2 (3)
7-8	4 (7)	1 (1)
9	1 (2)	...
14		1 (1)
22	1 (2)	...
Mean	2.2	1.1*
Standard deviation	3.6	2.1

*t=2.12, df=82, P<.05; degrees of freedom approximated for unequal sample variance.

cases were terminated at the investigative committee level. The difference between these groups in mean number of previous investigations was significant ($t = 2.12$, $df = 82$, $P < .05$). We found no relationship between the amount of time since the previous investigation and the outcome of the key complaint.

Discussion

To our knowledge this report is the first to focus on the problem of inappropriate prescription writing from the perspective of a state licensure board. We focus both on the subcommittee that investigates the more serious allegations and on the actions of the Oregon BME as a whole. The data take us into the decision-making process of the board, allow certain comments about the process, and provide insight into a part of the problem of inappropriate prescription writing.

Inappropriate prescription writing involving controlled drugs is clearly the most common problem brought before the Oregon BME. More than half the complaints are in this category, with suspected substance abuse a distant second at 13%. More than a third of the cases originate with the board's own investigators, who identify suspected problem cases through pharmacy checks. Because there is a limited number of investigators, these routine checks are neither systematically carried out nor evenly distributed throughout the state. We have no doubt that with more investigative resources, many more problem situations would be identified.

The BME's investigative committee treated complaints arising from its own investigators differently from those coming from outside sources. A significantly higher proportion of the BME-identified cases were reviewed by the whole board. We hypothesize that the investigators, knowing the board members and how they may have analyzed cases in the past, only selected the more serious cases from those they screened. The investigative committee also sends on to the full board significantly more physicians with previous investigative committee appearances, and the most frequent reason for previous investigations was the same as the key complaint—inappropriate prescription writing. It is important to note that most suspected cases of inappropriate prescription writing are brought to the attention of the BME by regulatory agencies. Patients and families, perhaps for self-serving reasons, are not likely to complain.

Most of the physicians in this sample are men, graduates of American medical schools with a mean age of 54. Nearly 75% of the sample are aged 40 to 70 years and, on average, they graduated from medical school 26 years before the time of their key complaint. Thus, in general, they fit the profiles of physicians with high prescribing rates. It should be emphasized, however, that 15% were younger than 40 and 28% of this group already had previously been investigated. Most (65%) were either in general practice, family practice, or internal medicine. Although we had no specific data on practice setting, these physicians were most likely primary care physicians. As such, they may be more vulnerable to potential inappropriate prescribing practices. Chronic pain was the leading patient complaint, and opiates were far and away the most frequently mentioned drugs, with benzodiazepines also commonly cited.

We found few clearly dishonest physicians in our sample; only 6 of 130 were also investigated for unprofessional conduct. Physicians disabled by substance abuse were also uncommon. Only 8 investigations of alleged substance abuse were encountered in our sample of 130. While substance-abusing physicians frequently prescribe inappropriately, they appear to account for only a small portion of our sample. Physicians with inadequate pharmacologic knowledge, usually revealed in their correspondence with the board, seemed more common. Finally, the high rate of recurring complaints, including several physicians who knowingly wrote prescriptions that violated voluntary restrictions, suggests that viewing these physicians as duped is too simplistic an explanation. A subtle form of psychological vulnerability might be an important factor in the inappropriate prescribing of psychoactive drugs.

After reviewing charts, observing interviews, and talking with board members and study subjects, we have repeatedly found evidence of a syndrome we call the "pseudobenevolent overprescriber," which is characterized by four factors:

- A strong and deeply felt need to help;
- A touch of grandiosity and omnipotence typified by statements like "Only I am capable of helping or likely to help this patient";
- An orientation towards immediate symptom relief that overshadows a consideration of long-term consequences; and
- An inability to handle his or her own feelings if the treatment that could provide immediate relief is withheld. Associated characteristics include a sense of being a patient advocate and a tendency towards expedience in the service of what the physician thinks the patient needs.

These factors may all promote the physician's self-image as a benevolent and powerful figure. The pseudobenevolent overprescriber's characteristics often seem to coexist with inadequate pharmacologic knowledge. They sometimes may be reinforced outside the physician's conscious awareness by the economics and time pressures of practice or by self-serving, manipulative, psychiatrically disturbed, or substance-abusing patients who reinforce these characteristics for their own ends. We offer this tentative characterization as potentially useful in guiding further studies of the problem, including the associated issues of an early identification of at-risk physicians and educational approaches to prevent or minimize the problem.

The extreme rarity of complaints of inappropriate prescribing of noncontrolled drugs in this study requires further

examination. Many other drugs are misused commonly, with a variety of detrimental effects. Perhaps most studied is the problem of inappropriate antibiotic use in patients in hospital. Such problems may be especially difficult to detect using pharmacy record reviews. The sheer volume of prescribing of controlled drugs resulted in the attention of the BME in many cases. Such volume is seldom seen with other types of drugs. Also, without both substantial medical knowledge and knowledge of an individual case, an inappropriate use of medications such as antibiotics will not be detected. Noncontrolled drugs do not cause dependence and hence do not tend to promote their own use. Finally, few patients knowingly deceive physicians to receive antibiotics, though certainly some will to receive controlled drugs. Thus, the low frequency of reports of overprescribing noncontrolled drugs likely reflects both the limits of the detection methods used by the BME and characteristics inherent in most controlled drugs.

The importance of an expanded focus on inappropriate prescribing is obvious—such prescribing may cause substantial iatrogenic harm. With controlled drugs, in particular, it may contribute either wittingly or unwittingly to a patient's diversion into illegal distribution networks, to psychological and physical dependency, and to overdose. The costs of such iatrogenesis, both directly through the expense of the inappropriate treatment and the consequent medical and rehabilitative treatment that may be required, and indirectly through impaired occupational and social functioning, are enormous.

The Oregon BME was able to identify and review a surprisingly large number of complaints of inappropriate prescribing of controlled drugs. Our study provides preliminary suggestions about the physician characteristics that promote such problems. These data also show, however, that identifying improper prescribing of other drugs is extremely difficult using the methods and sources available to even the most active boards of medical examiners. Continued work on identifying and correcting patterns of misprescribing all types of drugs is crucial.

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Medical Education

Western Medical Schools—A Breed Apart

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Based on the Presidential Address at the annual meeting of the Western Association of Physicians in Carmel, California, February 16, 1988.

The 16 medical schools in the 13 western states are distinctive from their counterparts nationally in several ways: they are relatively young, enroll a small number of medical students, and tend to be strongly research oriented. The rise of these institutions since Abraham Flexner's visit to all of the western schools in 1909 reflects a truly remarkable development.

(Dale DC: Western medical schools—A breed apart. West J Med 1989 May; 150:602-603)

There are now 127 medical schools in the United States; 16 are located in the 13 western states (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming). By comparison with other regions, the western schools are distinctive in several ways. They are relatively young, and they are predominantly publicly supported. They enroll a relatively small number of students and tend to be research oriented. They also now cooperate in a number of activities: support of the annual western clinical research meetings in Carmel, California—the Western Section of the American Federation for Clinical Research, the Western Society of Clinical Investigation, and the Western Association of Physicians—sponsorship of the clinical investigation section of THE WESTERN JOURNAL OF MEDICINE, and regional medical education activities coordinated by the American Association of Medical Colleges.

The oldest medical school in the West is the University of California at San Francisco, which opened in 1864. Only three other present-day schools—the University of Colorado (1883), the University of Southern California (1885), and the University of Oregon (1887)—date from before the turn of the century. Three others—the University of Utah (begun as a two-year school in 1905), Stanford University (1908), and Loma Linda University (1909)—were opened before the Flexner report on medical education in the US in 1910.[1]

The Flexner report provides an interesting perspective and a useful benchmark for examining early medical education in the West. At the turn of the century there were then nearly 160 medical schools in the US, including 15 western schools. In April and May of 1909, Flexner visited all of them—ten medical schools in California, two in Colorado, two in Oregon, and one in Utah—under the auspices of the Carnegie Foundation, spending about a day at each school.

Even before his trip to the West, Flexner was firmly convinced that there were too many medical schools in the United States giving too low a quality of education and that overall the country had too many poorly trained physicians. With his visit, he found this to be a particularly serious problem along the West Coast. California then had 240 doctors per 100,000 population, a number not very different from the current level of 262 physicians per 100,000 population. In his summary report, he recommended reducing the number of schools nationally to 31, with only 4 western schools, 1 each in Denver, Salt Lake City, San Francisco, and Seattle.

In his report, Flexner commented favorably on only a few schools: the University of California at San Francisco and Berkeley, the University of Southern California, the University of Colorado, then at Boulder, and the new two-year school of the University of Utah. In general, he deplored conditions elsewhere, particularly in the proprietary schools. He reported that at the California College of Medicine in Los Angeles, 26 of 27 faculty members held the rank of professor; he found that the weaker schools were often top heavy with professors. At the University of California at San Francisco, he thought that the clinical teachers, except perhaps for the dean, were not in touch with laboratory work and ideas as were taught in the basic sciences at Berkeley. He was concerned about the quality of clinical teaching. For the University of Colorado, he noted that the medical school was then receiving 14% of the University's total state support, but in Oregon the school was receiving only $1,000 per year, far too little for an adequate school. He commended the state of Washington for not beginning a medical school as they could not afford one. He also did not believe that the Denver and Gross College, a private medical school in Denver, would be able to attract sufficient students to fill its class after the state of Colorado passed a law in 1909 requiring that applicants for licensure have at least one year of college. He said, however, that this school could possibly continue if it trained "low grade men" for the adjacent states of Wyoming, Arizona, Idaho, and New Mexico, which lacked medical schools.

Rapid changes in medical care and the intense scrutiny that medical education received early in the 20th century prompted the closing of many medical schools, including 8 of the 15 western schools visited by Flexner. Furthermore, no new western schools were started until the end of World War II. The University of Washington (1945) and the Uni-

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versity of California at Los Angeles (1951), as well as the University of British Columbia (1950) were then opened and were followed by a second wave of new schools in the era of the Great Society—New Mexico (1961), Arizona (1962), California (San Diego, 1962; Irvine, 1962; and Davis, 1963), Hawaii (1967), and Nevada (1969). Of the 16 western schools, 13 (81%) are publicly supported, whereas for other regions, only 61 of 111 (55%) are public institutions.[2]

Medical schools can be studied and compared in many ways, for example, by the size of the entering class (Table 1). In general, medical school enrollment in the West has always lagged behind population growth by comparison with national averages. For instance, in 1986-1987, there were 1,752 first-year medical students (about 10% of the national first-year students) enrolled in the schools in the 13 western states, which have about 20% of the US population.[3] Of these students, 85% were from this region (the total of first-year western students in western schools was 1,489). There were, however, 1,338 students from the western states enrolled as first-year medical students in schools in other regions.[3] Thus, only about half (53%) of the students from the West going to medical schools are in western schools. There would need to be twice as many schools or the present schools would need to be nearly twice their current size if they were to accommodate all of the medical students from this region going to medical school.

A somewhat different picture emerges at the level of graduate medical education. For a long time there have been more internships (first-year residencies) in the West than there are graduates of the western schools. In 1987 there were 1,703 graduates for the region and 3,078 western internships or first-year residency positions available (16% of the national total).[4] Many of these positions date from the 1920 to 1950 period when graduate medical education programs were used to upgrade hospital care and to attract young physicians to the West. Most are now in urban centers and affiliated with medical schools. There are substantial variations in the locations of these positions. For instance, in Arizona there are nearly three graduate medical education positions for every medical student who graduates there, whereas New Mexico now has a ratio of graduate medical education positions to medical student graduates of less than 1.[4] On a state-by-state basis, all of the more populous western states have more first-year residency positions than graduating medical students, in contrast to many midwestern and southern states with relatively few graduate medical education positions. It can easily be seen that the schools can influence the location and specialty distribution of physicians practicing in the region through the graduate medical education program they sponsor as well as through medical student education. This is particularly the case in the West because both students and residents who have trained here tend to stay here.[5]

TABLE 1.—*Some Characteristics of Western Medical Schools, 1986-1987*

Characteristic	*West*	*United States*
Medical schools, No.*	16	127
Public funding, No. (%)	13 (81)	75 (59)
Private funding, No. (%)	3 (19)	41 (52)
Students, average No. per school*		
Medical students, No.	451	538
Residents, No.	599	498
Graduate students, No.	154	130
Students (total)*		
First year, No.	1,752	16,779
Graduating, No.	1,703	15,872
Resident positions—first year†	3,078	19,047
Faculty, average No. per school‡		
Total full-time faculty (FTE), No.	491	498
Associate professors and professors, No.	278	249
Principal investigators for research grants, No.	125	99
Research expenditures per FTE, $	56,000	32,000
Population, millions	48	239

*From Appendix II, Table 2, "Medical Schools in the United States," *The Journal of the American Medical Association* (1987; 258:1074-1077).[3]
†From National Residency Matching Program Directory.[4]
‡From Association of Medical Colleges.[6]

One other comparison of the western schools with those in other regions is particularly noteworthy. Statistics gathered by the Association of American Medical Colleges indicate that the western schools are more research oriented than those of any other region.[6] These data show that the percentage of faculty who are principal investigators for research grants is currently 24% for western schools versus 18% for faculty nationally. The percent of the schools' budgets that goes for research is also larger in the West (22% for western schools versus 17% nationally). Research expenditures for faculty are also substantially more. Because the sizes of the western basic science departments are slightly smaller—the average western basic science faculty numbers 106 per school versus 115 per school nationally—it may be inferred that more of the investigators and more of the research expenditures are in clinical departments in western schools. When reasonably consistent methods are used to compare the revenues of medical schools, the biggest difference between schools in the West and schools in other regions is the size of their research budgets.[6]

The growth and development of western medical schools since Abraham Flexner's visit 79 years ago is truly remarkable. The schools have become leaders in both basic and clinical research and have led the way in many innovative educational endeavors. They now compete favorably with their eastern counterparts in terms of the quality of their students and the prestige of their faculty. Their greatest challenge lies in maintaining the pioneering spirit that brought them so far so fast and the public support (both state and federal) on which they are now continually dependent.

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Information

Mucocutaneous Injuries at a University Teaching Hospital

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MUCOCUTANEOUS INJURIES, characterized by cutaneous or mucous membrane exposure to potentially infectious body fluids, represent a significant occupational health hazard for health care providers. Exposure may occur by the direct inoculation during injury to intact skin by sharp objects, such as hypodermic needles or surgical instruments, or by the surface contamination of mucous membranes or broken skin. Mucocutaneous injuries are important because they occur commonly, are preventable, and carry the risk of disease transmission.[1] Puncture wounds appear to present the highest risk for disease transmission, and infection by this route has been documented for viral hepatitis,[2] malaria,[3] tuberculosis,[4] lues,[5,6] and Rocky Mountain spotted fever.[7] Infection with the human immunodeficiency virus (HIV) has occurred by puncture wounds and contamination of broken skin and mucous membranes, although the risk appears to be low.[8-10]

Previous investigations have focused on needle-stick and puncture wounds, and increased risk for these injuries has been shown for nursing, housekeeping, and laboratory staff.[11-13] High-risk groups have been broadly defined, however, which may conceal pronounced variations in risk between subgroups. For example, the risk calculated for all nursing personnel represents an average of the risk for low-risk groups with infrequent patient contact, such as administrative nurses, and higher risk groups with frequent and intense patient contact, such as emergency department nurses.

The study of this occupational hazard has been hampered by several factors, including poor compliance with reporting requirements.[11] In addition, methods for calculating risks for health care workers have been inconsistent. Rates for needle-stick injuries have been calculated based on the number of injuries per employee per year,[14] injuries per full-time-equivalent employee (FTE) per year,[11] and number of injuries per hospital bed per year.[15] It has recently been suggested that the rates be calculated as the number of reports per 100 FTE per year based on actual paid productive work time—that is, excluding paid vacations and sick leaves—rather than the number of allocated employee positions.[16] The incidence rates calculated in this manner reflect the probability of an injury occurring over time in those at risk and are consistent with rate calculations used by the United States Department of Labor for other industrial sectors.[17]

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In early 1986 the Employee Health Service at the University of California, Davis, Medical Center (UCDMC) developed a new mucocutaneous injury report form and instituted an educational program emphasizing the prevention of injuries and the need to report those that do occur. This was associated with an immediate and sustained sevenfold increase in reports of mucocutaneous injuries per month compared with the preceding six months. We conducted a study of mucocutaneous injuries, including needle sticks, injuries from other sharp instruments, and contamination of broken skin or mucous membranes, reported after this program was implemented, and estimated the incidence rates based on US Department of Labor methods among occupational groups of hospital workers.

Subjects and Methods

The UCDMC, a 470-bed referral hospital, is a major tertiary care center for the metropolitan Sacramento area and a large portion of northern California. The UCDMC also serves a large indigent population from the Sacramento area. The hospital is the primary teaching hospital for the university medical school and several affiliated nursing programs. Clinical care units at UCDMC include general care wards, specialty intensive care units, a hemodialysis unit, and several outpatient facilities. The medical center employs about 4,000 persons, including more than 2,000 nurses, faculty, house staff, technicians, and ancillary personnel involved directly in patient care.

Hospital employees are instructed at the time of their initial employment and at periodic in-service training meetings in preventing mucocutaneous injuries. Employees likely to encounter potentially infectious body fluids are encouraged to be immunized with hepatitis B vaccine. Employees are advised to treat all body fluids as infectious, and the use of gloves is encouraged when handling fluid specimens. Employees are discouraged from recapping hypodermic needles after use and instructed to dispose of them in puncture-proof containers. These containers are available in all treatment areas and patient rooms, with the exception of the general wards, pediatrics areas, and psychiatry floors, where they are not generally available in patient rooms because of security concerns. Mucocutaneous injuries and other work-related injuries are to be reported to the Employee Health Service.

In early 1986 a revised mucocutaneous injury report form was distributed. The form requested information regarding the injury circumstances, location, and contact patient characteristics and provided instructions for first aid and follow-up with the Employee Health Service. Each injury was investigated by the Employee Health Service staff, and therapeutic measures were taken according to established policies based on Centers for Disease Control (CDC) guidelines.[18]

Data for this study were collected by reviewing the incident report forms and consulting employee health records of involved employees. Employment status, hospital census, and the sum of paid work time for specific job classifications were obtained from the hospital departments of finance, personnel, hospital information systems, and nursing. For hos-

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
FTE = full-time equivalent [employee]
HBsAg = hepatitis B surface antigen
HIV = human immunodeficiency virus
UCDMC = University of California, Davis, Medical Center

pital employees, productive paid work time was estimated as 87% of the total paid work time based on the productive fraction of total paid work time for nursing and other hospital employees during the period of the study. For registry nurses contracted through outside agencies, the productive work hours total was available directly from the nursing department. A total of 2,000 hours represented 1 FTE per year in accordance with US Department of Labor methods.[17]

Job-specific incidence rates were calculated for licensed vocational nurses, registered nurses, per diem nurses, intensive care unit nurses, emergency department nurses, operating room nurses, registry nurses contracted from outside agencies, and house-staff physicians. Rates were also calculated for housekeeping personnel, laboratory, surgical, medical, and radiology technicians, and hospital assistants (employees assisting in the preparation of patients, materials, and equipment for procedures). Incidence rates were expressed as the number of injuries per 100 FTE per year.

TABLE 1.—*Mucocutaneous Injury Reports by Job Description**

Job Description	Frequency n	Frequency (%)†
Nurses	238	(74)
Physicians	18	(6)
Hospital assistants	14	(4)
X-ray technicians	8	(3)
Police	8	(3)
Maintenance/housekeeping	8	(3)
Nursing students	4	(1)
Medical students	4	(1)
Surgical technicians	4	(1)
Laboratory technicians	2	(1)
Miscellaneous	12	(4)
Total	320	(100)

*Multiple injuries to the same employee are counted independently.
†Percentages will total more than 100 due to rounding.

Approximate 95% confidence intervals (95% CI) for the observed rates were calculated based on the square root transformation of the Poisson distribution.[19] After adjusting for job title, cases were compared with the hospital employee population profile during the midpoint of the study period. Signed rank and *t* tests were used to evaluate differences in the distributions of age, employment duration, sex, assigned shift schedule, full-time (>80%) versus part-time appointment, and career versus noncareer status. For these comparisons, the hospital employee population profile did not include students, physicians, police, or employees contracted from private registries. Analyses were done on a VAX 11/750 using the Statistical Analysis System software package.[20] The study protocol was approved by the University of California, Davis, Human Subjects Review Committee.

Results

A total of 320 mucocutaneous injuries involving 276 employees were reported between March 1, 1986, and November 30, 1986. The mean monthly report rate was 35.6 (range 26 to 47). No associations were detected between the monthly report rate and hospital census figures. In all, 81% of reports involved female employees. The mean age at the time of injury was 34.8 years (range 22.1 to 64.6 years), and the median duration of employment was 1.7 years (range 0 to 26.4 years). After adjustments were made for job title, persons reporting injuries had a shorter employment duration ($P<.01$), younger age ($P=.05$), and were more likely to have a variable shift schedule ($P<.01$) than the hospital employee population. No significant differences in the sex ratio or likelihood of full-time or career employment status were observed. Age, employment duration, and assigned shift schedule were strongly correlated. After a further adjustment was made for employment duration, cases no longer differed significantly from the hospital employee population with respect to age and the likelihood of having a variable shift schedule.

Nursing staff contributed 238 (74%) reports (Table 1). Physicians were the next largest group, accounting for 18 (6%) reported injuries. Of these injuries, 14 occurred in house-staff physicians. Incidence rates and 95% confidence intervals were calculated for selected job descriptions (Table 2). The highest incidence rate was for nurses (35 per 100 FTE per year; 95% CI, 30.7 to 39.6). Among the nurses, the

TABLE 2.—*Mucocutaneous Injury Incidence Rates* for Selected Job Descriptions*

Job Description	All Reports Incidence	All Reports (95% CI)	Needle-Stick Incidence	Needle-Stick (95% CI)
All nurses	35	(30.7-39.6)	27	(23.2-31.0)
Operating room nurses	67	(41.4-98.7)	10	(1.9-24.5)
Per diem nurses	48	(26.8-75.4)	41	(21.7-66.3)
Intensive care nurses	40	(28.8-53.0)	33	(23.0-44.8)
Registered nurses	40	(34.6-45.8)	31	(26.3-36.1)
Emergency department nurses	38	(21.7-58.9)	28	(14.4-46.1)
Registry nurses	31	(18.3-47.0)	22	(11.7-35.6)
Licensed vocational nurses	26	(17.7-36.0)	18	(11.3-26.3)
Administrative nurses	9	(3.2-17.6)	9	(3.2-17.6)
Technicians (x-ray, clinical laboratory, surgical, medical)	13	(7.3-20.4)	6	(2.4-11.3)
Hospital assistants	12	(6.5-19.1)	8	(3.6-14.1)
House-staff physicians	6	(3.3- 9.6)	5	(2.6- 8.2)
Maintenance/housekeeping	5	(1.9- 9.5)	5	(1.9- 9.5)

*Incidence rates are calculated as the number of injuries per 100 full-time-equivalent employees per year.

TABLE 3.—*Injury Type by Location*

Injury Type	Location: Intensive Care Units n (%)*	General Care Ward n (%)*	Operating and Recovery Rooms n (%)*	Emergency Department n (%)*	Other n (%)*	All Locations n (%)*
Needle-stick injury	61 (81)	106 (85)	14 (32)	21 (62)	34 (79)	236 (74)
Other sharp instrument	0 (0)	4 (3)	17 (39)	2 (6)	3 (7)	26 (8)
Contamination of broken skin or mucous membrane	13 (17)	4 (3)	8 (18)	8 (24)	1 (2)	34 (11)
Unclassified	1 (2)	10 (8)	5 (11)	3 (9)	5 (12)	24 (8)
Total†	75 (100)	124 (100)	44 (100)	34 (100)	43 (100)	320 (100)

*All percentages refer to the respective columns.
†Percentages do not always total 100 due to rounding.

operating room staff showed the highest rate at 67 per 100 FTE per year (95% CI, 41.4 to 98.7). Per diem nurses had an incidence rate of 48 per 100 FTE per year, compared with incidence rates of 38 per 100 FTE per year for emergency department nurses and 40 per 100 FTE per year among intensive care unit nurses.

In all, 35 persons reported more than one injury during the period of the study (range, two to four reports). These persons represented 13% of involved employees and were responsible for 79/320 (25%) reports. Employees reporting more than one injury during the course of the study did not differ significantly from employees generating a single report with respect to age, sex, duration of employment, or type of injury.

Of the 320 reported cases, 236 (74%) represented needle-stick injuries, 34 (11%) involved contamination of broken skin or mucous membrane surfaces with potentially infectious body fluids, 26 (8%) involved sharp instruments other than injection needles, and 24 (8%) were unclassified (Table 3). The most frequently reported injury location was the general care wards, where 124 (39%) injuries were reported. The type of injury varied with location. Needle-stick injuries constituted more than 60% of reports in all locations except the operating and recovery rooms, where injuries with other sharp instruments predominated. Contamination of broken skin or mucous membranes with body fluids was the second most frequent injury after needle sticks and was most common in the emergency department, operating and recovery rooms, and intensive care units.

Among the 236 needle-stick injury cases, intravenous or intramuscular injections or phlebotomy was associated with 139 (59%) of the reported incidents (Table 4). Needle recapping or disposal accounted for 25% of the needle-stick injury reports. Of the 34 reports of contamination of broken skin or mucous membranes, 18 (53%) involved splashes to the eyes, frequently while doing endotracheal suction.

One or more risk factors for hepatitis B[18] were reported in contact patients for 110 (34%) incidents (Table 5). The single most common risk factor was a history of multiple transfusions, reported in 54 (17%) cases. Multiple risk factors for hepatitis B in the contact patient were noted in 19 (6%) reports. The highest prevalence of hepatitis B risk factors in contact patients was noted in the emergency department, where risk factors were reported for 15 (44%) of 34 injuries. Serologic tests for hepatitis B surface antigen (HBsAg) in the contact patient were positive in 10 (5%) of 207 tested cases. Positive serologic evidence of HBsAg was found in 8 (10%) of 78 tested contact patients with reported risk factors for hepatitis B. The acquired immunodeficiency syndrome (AIDS), AIDS-related complex, or serologic evidence of HIV in the contact patient was noted in 9 (3%) reports.

Proper first-aid procedures, consisting of assiduous scrubbing of the affected area, were carried out by the employee in 293 (92%) cases. Hepatitis B vaccination was recommended in nonimmune employees in 30 cases; 6 employees declined the vaccine. Hepatitis B immune globulin was given in 19 cases; 17 (89%) of the employees receiving the vaccine were eligible to receive prophylactic hepatitis B immunization as an employment benefit at no charge but had not availed themselves of it before the reported injury. Immune serum globulin was given in two cases. The single reported complication was an episode of conjunctivitis following a body fluid splash to the affected eye; this condition resolved with topical antibiotics. This case was self-reported by the involved employee. No active follow-up was done to document complications following injury or therapy.

Discussion

Mucocutaneous injuries represent a common occupational health hazard for certain groups of health care providers. The experience in our medical center shows that nursing staff had the largest number of reported injuries and nurses were at greater risk than employees in other job categories. Needle-stick injuries predominated in all hospital locations except the operating and recovery rooms, where injuries with other sharp instruments were more common. Contamination of broken skin or mucous membranes with body fluids was more common in the operating and recovery rooms, emergency department, and intensive care units than in other settings. Risk factors for hepatitis B were present in 34% of reported cases and were reported most frequently in the emergency department patient population.

Among the nursing staff, operating room nurses showed the highest risk. The predominant type of mucocutaneous injury for operating room nurses involved injuries with sharp instruments other than needles, such as saw blades, scalpels, and other surgical cutting instruments. The reasons for the increased risk are not clear, but safety problems inherent in the design of the instruments and the presence of many health care personnel working in a relatively confined space may be important factors. Compliance with reporting of injuries may also be greater in this group of nurses.

It is likely that underreporting has resulted in an underestimation of the actual incidence rates for mucocutaneous injuries. Underreporting, or failing to report incidents, is common according to other investigators. Hamory carried out a questionnaire survey and found that 40% of needle-stick injuries occurring in the preceding three months at a

TABLE 4.—*Activity Associated With Reported Injuries*

Activity	Injury Source: All Injuries n	(%)*	Needle-Stick Injuries n	(%)*	Other Sharp Instruments n	(%)*	Mucocutaneous Contamination n	(%)*	Other n	(%)*
Intravenous/intramuscular procedure	77	(24)	76	(32)	0	(0)	1	(3)	0	(0)
Phlebotomy	65	(20)	63	(27)	1	(4)	0	(0)	1	(4)
Needle recapping	34	(11)	34	(14)	0	(0)	0	(0)	0	(0)
Handling surgical instrument	30	(9)	7	(3)	21	(81)	2	(6)	0	(0)
Handling trash or linens	25	(8)	21	(9)	2	(8)	0	(0)	2	(8)
Sharp instrument disposal	24	(8)	24	(10)	0	(0)	0	(0)	0	(0)
Major bedside procedure	5	(2)	4	(2)	1	(4)	0	(0)	0	(0)
Other or unspecified	60	(19)	7	(3)	1	(4)	31	(91)	21	(88)
Total†	320	(100)	236	(100)	26	(100)	34	(100)	24	(100)

*All percentages refer to the respective columns.
†Percentages may exceed 100 due to rounding.

TABLE 5.—*Reported Risk Factors for Hepatitis B in Contact Patients*

Risk Factor	Frequency n	(%)
No known risk factors	172	(54)
Patients with risk factors*	110	(34)
Multiple blood transfusions	54	(17)
Intravenous drug abuse	31	(10)
Asian immigrant	13	(4)
Acute hepatitis	12	(4)
Documented AIDS, ARC, or positive HIV serology	9	(3)
Male homosexual	9	(3)
Institutionalized for Down's syndrome	1	(<1)
Dialysis patient	1	(<1)
Patient source unknown	38	(12)

AIDS=acquired immunodeficiency syndrome, ARC=AIDS-related complex, HIV=human immunodeficiency virus

*Multiple risk factors in the same patient are counted independently.

university hospital were not reported.[11] The likelihood of reporting an incident may be influenced by the circumstances of the injury, the hospital location, the job description, the level of training of the involved employee, and the attitude of the hospital staff toward reporting. Underreporting is particularly common among physicians.[1] This study was not designed to estimate underreporting rates; however, the sevenfold increase in the monthly rate of reported injuries noted after instituting the hospital program to improve reporting suggests that underreporting has been substantially reduced.

Reporting bias may also affect the results of this study. Employees may be less likely to report exposures viewed as minor or incidents that do not involve contact with patients with known risk factors for hepatitis B or HIV. These data may therefore be biased in representing cases perceived as more serious by employees. The immune status of an employee may also affect reporting. Persons who have been vaccinated for hepatitis B may be less likely to report incidents if they feel they are protected against the virus. Reporting bias may have contributed to the observation of a higher prevalence of risk factors for hepatitis B in emergency department patients. Concern that viral hepatitis and other diseases may be more likely in an emergency department patient population could lead to a more careful search for risk factors in this group compared with other hospital settings. The lack of a control group of employees not reporting injuries in this study makes it impossible to evaluate quantitatively the influence of underreporting and bias. We do not think, however, that bias explains adequately many of these findings, such as the sevenfold differences in observed injury rates between various nursing job categories.

The results of this study confirm and expand on those of other authors. Previous investigators have shown that nurses are at high risk for needle-stick injuries.[11-15,21] Estimates of the annual risk for nurses have varied depending on the methods used in the study. Hamory estimated an annual risk for needle-stick injuries in nurses of 61.1 per 100 FTE based on questionnaire responses.[11] Other investigators have estimated risks ranging from 8.5 to 28 per 100 FTE based on employee health service records.[12-14,16,21] Only one study presented incidence rates calculated based on US Department of Labor methods. Fishman and co-workers calculated rates for needle-stick injuries among nursing staff of 9.3 and 28.0 per 100 FTE per year at two community hospitals. The rate of 27 per 100 FTE per year for needle-stick injuries in nurses observed at our hospital is consistent with these results.

An increased risk for needle-stick injury has also been documented in laboratory and housekeeping personnel.[11,12] Risk estimates of 25.5 and 34 per 100 FTE have been calculated for laboratory and housekeeping workers, respectively, based on questionnaire responses.[11] We noted risks of 6 per 100 FTE for technicians, including clinical laboratory personnel, and 5 per 100 FTE for housekeeping workers. Other authors using employee health service records have observed higher rates ranging from 6.7 to 18 per 100 FTE in these workers.[12-14,21] The reasons for the lower risks observed in our study are unclear; possible differences in complying with needle disposal precautions or underreporting by these groups in our institution may contribute.

Persons reporting mucocutaneous injuries in this study had a shorter employment duration than the hospital employee population. Similar findings were reported by Hamory.[11] Other investigators have found an increased risk for part-time and night-shift personnel.[21] No adjustment was made for employment duration, however. Our data suggest that employment duration may be an important confounding factor. At our hospital, new employees are more likely to have variable shift schedules and to have noncareer, part-time positions. After accounting for job title and employment duration, no significant differences in shift or the likelihood of being a noncareer or part-time employee were noted. An increased risk for newer employees is likely related to inex-

perience. In addition, newer employees may be more likely to follow hospital reporting policies for injuries.

The distribution of mucocutaneous injury type and contact patient risk factors by hospital location has not been previously reported. The increased proportion of contamination injuries in the intensive care units, operating and recovery rooms, and emergency department indicates a need for more health education efforts and protective measures in these areas to prevent contamination exposures. In particular, the use of protective eye coverings and gloves when handling body fluids or doing endotracheal suction is warranted. For needle-stick injuries, intravenous and intramuscular procedures and phlebotomy were associated with most of the reported injuries, and in-service training should focus on the proper technique for these procedures. Design improvements minimizing the potential for contact with hypodermic needles can also play an important role in reducing needle-stick injury rates in the future.[22]

An important finding of this study is that of increased rates among per diem nursing staff. At our institution, per diem staff are frequently used in a "float" capacity, requiring them to work in various locations within the hospital. The changing duties and work locations experienced by this group may play a role in their higher injury rates. In some hospitals per diem nurses are not eligible for employee benefits, including prophylactic hepatitis B vaccine. Although immunization is recommended, its cost must be borne by the employee. These data support extending coverage for prophylactic hepatitis B vaccination as a benefit for all high-risk employees, whether or not they qualify for the standard employee benefits package. These findings also underscore the importance of doing HBsAg serologic tests in contact patients, in accordance with CDC recommendations.[18] The prevalence of a positive test in patients with risk factors for hepatitis B was 10% in this study. It is likely that most employees given hepatitis B immune globulin (approximate cost of medication, $90 per injection) because of the risk status of the contact patient would not have required this therapy if serologic testing for HBsAg (approximate cost, $50) had been done for the contact patient.

Based on these data, preventive measures for mucocutaneous injuries should be targeted toward high-risk job categories and locations within a hospital generating large numbers of incident reports. In our hospital this includes the nursing staff of the general wards and acute care areas such as the intensive care units, operating and recovery rooms, and emergency department. Prophylactic vaccination should be encouraged for high-risk persons in accordance with CDC recommendations. The proper technique in the handling of body fluids and sharp instruments and the importance of reporting incidents should be emphasized, particularly among new employees. Determining the HBsAg status on contact patients will allow practitioners to avoid the expense and potential complications of administering hepatitis B immune globulin in most such exposures.

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Lessons From the Practice

The Importance of Hope

ALEXANDRA M. LEVINE, MD, *Los Angeles*

A hundred years ago, when I was a medical student on the general medicine wards, a 55-year-old woman was admitted to my service with a coin lesion in the right upper lobe of the lung. She was basically well and asymptomatic and spent the next week undergoing diagnostic studies—bronchoscopy and so forth. During that time, I got to know her and like her. She was a real dynamo, vigorous and friendly. She became the extra pair of hands on the ward, helping to pass the meal trays, running minor errands. We all came to love her. When the diagnostic tests came back nondiagnostic, the patient was transferred to the surgery service and underwent an open thoracotomy. At operation, she was found to have a squamous cell carcinoma that had already invaded the mediastinal nodes, such that the tumor was not resectable. A biopsy was taken, and the incision was closed.

I was dreading the next morning; I was afraid to see her because I didn't know what to say—what words to use. I chose to wait, and I went into her room for the first time with the resident and interns. The resident stood at the side of her bed—think of that for a moment—stood there, looking down at her—not looking at her—try that sometime. I will tell you that it feels bad to have someone standing over you as you are lying in bed or sitting in a chair, talking down to you. In any event, he stood there and said, "Well, it's cancer, and we couldn't really resect it, so we just opened and closed." She asked, "Opened and closed?" He said, "Yes, well, it couldn't be removed, so we just closed." She kept repeating the words to him, and he kept nodding his head and confirming what he had said. "You mean you left the cancer there?" "Yes." She closed her eyes, said that she was tired, and the team walked out of the room.

When I went back to see her, she gave me a little small talk, but basically, she was just not the same person, and I was too young and inexperienced to know what to do. When I came in the next morning, I learned that she had died during the night. She was taken to autopsy, but there was no actual specific cause of death—just the cancer, which most certainly had been there for many months.

I have never been able to get her words out of my mind, "You opened and closed? You mean you left the cancer there?" I don't really know why she died, but to be honest, I will always believe that she died because all hope had been taken away from her. And I also believe that the key in that case was that the resident had said to her that she had cancer and that there was nothing that could be done. He obviously had taken her through a major operative procedure, and she had the pain and the scar to prove it, but nothing had been done. Furthermore, the resident never mentioned to her or suggested in any sense that there was any other treatment that could be used. His words took away her hope, and I honestly believe, as crazy as it may seem, that those words took away some of her potential lifetime.

Should he have lied to the patient? No, I don't think so, but I do think that we can be sensitive to the effect of our words, and that it might be acceptable to state the facts in such a way that we do not take away all possibility of hope. For example, why couldn't the resident have said that he removed some of the tumor but could not remove all of it, and, therefore, that further therapy would be required. That's all; that's not a lie. It states the facts as they occurred but still allows the patient some space in which to work, some possibility of life ahead.

Let me give one more example of this concept of hope, to illustrate that even if the patient does die, the time that he or she is given will be spent better if the patient has been allowed some hope, as opposed to spending the remaining lifetime in a state of perpetual fear that each day is supposed to be the last.

In 1982 a 30-year-old attorney was referred to me with a diagnosis of T-cell immunoblastic sarcoma. He had seen several physicians who had basically said to him—or at least he had heard—that this was a very aggressive disease, that he would require aggressive, multi-agent chemotherapy, but despite the therapy, they did not really believe his chances of long-term survival were very good. He came into my office with his mother and father—lovely people, all of them—and I basically agreed that he did have T-immunoblastic sarcoma, that he would require multi-agent chemotherapy, but here the story changed a little. I told him that this treatment had been able to cure some people—that was true. I told him that I didn't know whether or not he would be the one to be cured, but that even if the chance for that was only 1%, if he was the 1%, then the fact remained that the chance would be 100% for him. Since I really had no way of predicting whether or not he would make it, and since there was no question at all that long-term survival was a possibility, then why didn't we just assume that he was going to do well, and why didn't we just go for it, with a positive attitude and a good fight.

Well, we did go for it, and he went into remission, which lasted about a year. It was a good year. I knew it, and he knew it, and his folks knew it. At the end of the year, he relapsed, and he died several months later. Years have passed, and whenever I call his mother, consistently, every time, she has always begun our conversation by thanking me profusely for having allowed Paul to live that year instead of dying that year. It's a real subtlety, but it means everything.

(Levine AM: The importance of hope. West J Med 1989 May; 150:609)

From the Department of Medicine, University of Southern California School of Medicine, Los Angeles.
Reprint requests to Alexandra M. Levine, MD, USC School of Medicine, 1975 Zonal Ave KAM #500, Los Angeles, CA 90033.

Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Bag Balm and Duct Tape—Tales of a Vermont Doctor

Beach Conger, MD. Little, Brown and Company, 34 Beacon St, Boston, MA 02106, 1988. 263 pages, $16.95.

Is there a doctor among us who hasn't at one time or another cried out at the anguish of his urban practice, vowing that,

> For two cents I'd pack it all in, pick up my family, gather together the kit and caboodle, and head for the back country!
>
> There I could go back to the simple life, practicing medicine the way it should be practiced, with grateful patients who would accept me for what I am—a good doctor interested only in rendering top-notch patient care.
>
> No more insurance forms, no stupid Medicare rejections. No more dancing to the tune of JCAH requirements. I'll be rid of PRO watching over my shoulder. Farewell, as well, to those endless committee meetings.

That's what Beach Conger said, and that's what he set out to do. This internist, a Harvard Medical School graduate, after practicing in Atlanta and San Francisco, had finally gotten his belly full of "big city medicine." He yearned to embark on a new and different life and started looking for a way out.

During this search he impulsively answered a little classified ad he ran across in a medical journal, and almost before he knew it, he had landed in a charming Vermont village with the unlikely name of Dumster. Here was the town in which he was destined to practice within the wooden walls of a primitive hospital, where the room rent for a day was $25, all amenities included. Later, this was to be replaced by Emmeline Talbot Memorial Hospital, brought into being without the help of a dime of government money but with the generous contribution of dollars and sweat by the townspeople. The room rate had to go to $37.50, with an abundance of tender, loving care thrown in.

The plan was for Doctor Conger to gradually take over the practice of Old Doc Franklin, who after 40 years in the harness was ready to "slow down a bit." Perhaps it was fortunate that "Old Doc" wasn't as yet quite ready to turn all his beloved patients over to "New Doc." That gave Conger, whose love of writing was second only to his love of medicine, time to keep a diary, in which he began recording the daily happenings in the practice of medicine and surgery in Dumster, Vermont.

Life for the "New Doc" wasn't always as idyllic as he might have hoped. Sure, he was able to grow tomatoes and chop down some trees, but as the months rolled by he found himself consumed by the comings and goings, the diseases and disorders of his fellow citizens.

With the help of such colorful characters as Aaron Penstock, Buffy Uprite, and Harold Purlife, Doctor Conger managed to accumulate a bundle of amazing and amusing yarns about people in all walks of Dumster life. This is a tale filled with fascinating events that involve a physician in Small Town, USA. It might just as well have been Troy, Montana; Rock Springs, Wyoming; or even Coeur d'Alene, Idaho.

Beach Conger's characters are always real and mostly lovable. The stories are humorous, sometimes hilarious, and often heart-warming. He writes about Old Doc Franklin's Green Pill for Flatulence, and Mom Franklin's Elixir for Colic. And about broken legs and broken hearts.

There is Hiram Stedrock's private problem with his "male trouble" (his prostate), described by the patient in laconic Vermont vernacular with three words, "It don't work."

Mr Stedrock also provided the name for the book. When Hiram accidentally sliced his thigh with his chain saw, he tried to repair the gaping wound by pulling it together with duct tape covered with a generous smearing of bag balm, the favorite emollient of backwoods Vermonters.

When Hiram finally consented to come in to Doc Franklin for the necessary surgery, Old Doc's terse entry in the office ledger was:

> Tried to make his leg into kindling.
> Damn near did.
> Forty-two stitches.

Even when Conger writes about his struggles with various bureaucracies, he does it without bitterness. He writes with sadness when he comments on the arrogance that is bred into young physicians during their residency training, but he derides gently. As he practices honest medicine back there in Dumster, he is able to view the big picture of medical practice. He does it from the perspective of a big city specialist happily transformed into a plain but good country doctor who had finally "gotten the hang of it."

Beach Conger uses words so well. As he comments on the birds of various feathers who come to roost in the medical community, he singles out special creatures such as Doc Franklin.

> Easily identified by a telltale shock of white hair, he is truly an elegant bird. His feathers have been smoothed by the winds of time, and his talons, blunted by the grabbing of death's stony ground, are no longer dangerous. He looks more the protector than the predator; a source of comfort, not a cause for fear. When perched he appears almost tame.

What a delightful little book this is. *Bag Balm and Duct Tape* is just what the doctor ordered for a quiet evening before the fire or as a gift for a young student who might be thinking of becoming a physician.

Might we even dare to put this revealing treatise out in our waiting rooms for our patients to read?

E. R. W. FOX, MD
Coeur d'Alene, Idaho

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INTERNIST BE/BC to join growing practice in Tacoma, Washington. Practice is oriented to women's health issues. Women encouraged to apply. Send CV to PO Box 2122, Gig Harbor, WA 98335; (206) 858-8686 evenings.

OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294, or 1 (800) 234-1231.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; telephone 1 (800) 544-1987.

BC/BE GENERAL INTERNISTS needed for multispecialty group in Sacramento, California. We are an established Department of Medicine with close university affiliation. Pleasant practice setting where physicians are free to practice the highest quality medicine with full access to diagnostic, therapeutic, and consultative services. Our patients are from a growing Sacramento community with a good cost of living. Our hospital provides a substantial part of University of California Davis residency training program. Excellent in-house continuing medical education program. We are a successful, stable medical group experiencing robust growth. Outstanding starting salary and advancement. Full benefits and retirement. This is a quality career opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, 2025 Morse Ave, Sacramento, CA 95825.

PHYSICIANS WANTED

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

IDAHO. Opportunity for high quality of life, low cost of living in beautiful Idaho—sunbelt of the Pacific northwest. Join Family Practice teams at one of six multi-site community/migrant health centers providing primary care to rural communities. Outstanding four-season recreation, malpractice insurance paid, generous continuing education, competitive salary and benefits, loan repayment potential, and opportunity to provide OB services. Send résumé to Dean Hungerford, Idaho Primary Care Association, PO Box 6756, Boise, ID 83707; or call (208) 345-2335.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall 1988. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

OB/GYN, NORTHERN CALIFORNIA. Position available for BE/BC OB/GYN in 10 person department with new LDR suite, family centered Obstetric practice as well as full Gynecology practice. 20 miles south of San Francisco, adjacent to large wooded areas, and easy access to ocean. Prepaid medical group with competitive salary and very generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

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ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

INTERNAL MEDICINE. San Francisco bay area—immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical housestaff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

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FACULTY POSITIONS. The San Jose Medical Center Family Practice Residency Program has an opening for full-time and part-time faculty. Positions include direct patient care (including OB), resident teaching and administrative duties. Program affiliated with Stanford University School of Medicine. Competitive salary and benefit package. Please direct inquiries to Robert Norman, MD, Director, 25 N. 14th St, Ste 1020, San Jose, CA 95112; (408) 977-4507.

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ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Norman Olson, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

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SAN FRANCISCO BAY AREA. Family Physician or Internist wanted to join newly formed women physician group. Competitive salary with malpractice coverage, vacations and sick leave, and disability insurance. Send CV to Number 152, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN—IMMEDIATE OPPORTUNITIES for BC/BE physicians in northern California. Excellent salary compensations with benefits. Also private practice available in San Francisco area suburb. Please send CV or call Mary Frances Malone, Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

INTERNIST. Live and work in the beautiful Sierra foothills. Four busy Internists are looking for fifth. Easy access to San Francisco bay area, Tahoe, great outdoors. Contact Bob Hartmann, MD, 815 Court St, #7, Jackson, CA 95642; (209) 223-3837.

OREGON. General Internist (BC/BE) sought for busy practice. 10 member multispecialty group. Beautiful rural community. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

SAN FRANCISCO BAY AREA

BE/BC Internist. We currently are seeking highly qualified Internists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV:

Winslow Wong, MD
Chief, Department of Internal Medicine
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

(Continued on Page 617)

The benefit of antianginal protection plus safety...

CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

- **A remarkable safety profile**[1-6]
  The low incidence of side effects with Cardizem allows patients to feel better.
- **Protection against angina attacks**[1,5,7-9]
  The predictable efficacy of Cardizem in stable exertional and vasospastic angina allows patients to do more.*
- **A decrease in myocardial oxygen demand**
  Resulting from a lowered heart rate-blood pressure product.[5]
- **Compatible with other antianginals**[6]†
- **Safe in angina with coexisting hypertension, COPD, asthma, or PVD**[1,3,5,6]

60 mg GREATER DOSAGE FLEXIBILITY 90/120 mg

**CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.*

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

1419H8

CARDIZEM® ANTIANGINAL PROTECTION PLUS SAFETY

diltiazem HCl/Marion

Usual maintenance dosage range: 180-360 mg/day

Rx

Cardizem® (diltiazem HCl)

☐ 60 mg ☐ 90 mg

☐ 120 mg

Sig: tid

BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic	Petechiae, pruritus, photosensitivity, urticaria
Other	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

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(Continued from Page 614)

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

WASHINGTON. BC/BE Family Physician for a clinic-based immediate care center. The clinic is a 32 physician multispecialty group. Guaranteed income with excellent benefit package. Ideal opportunity for active practitioner who wants to slow down. Send CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

INTERNAL MEDICINE. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an Internist for full-time work. Competitive salary. Excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

FAMILY PRACTITIONER. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks a Family Practitioner for full-time work. Competitive salary. Excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- **OB/GYN.** Establish private practice with no investment. Guaranteed income. Hospital has newly designed Single Room Maternity Care and new Women's Health Center.
- **FAMILY PRACTICE.** Guaranteed income while you develop your own private practice. Share beautiful office with young, BC Family Practitioner in a flourishing practice. No investment required.
- **INTERNAL MEDICINE.** Guaranteed income while you develop your own private practice in association with an established practice. No investment required.
- **GENERAL/THORACIC SURGERY.** Establish private practice with no investment, guaranteed income. Excellent opportunity to do General and Thoracic Surgery—no open heart.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient.

Located in central California near Sequoia National Park, Tulare offers a family oriented environment, abundant and varied recreation, good schools, restaurants, and shopping. Beautiful, affordable homes close to hospital and office. Strong economy. New businesses are contributing to the steady growth of our active community which combines the life-style advantages of a small city with easy access to all California attractions.

Contact:

Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

FAMILY PRACTICE. Fantastic opportunity for the right physician! We operate six community health centers in central California. Currently we have two openings. One is for a fourth provider at our Wofford Heights Clinic located in a beautiful mountain lakeside resort. The second opening is in Frazier Park, a mountain resort area located one hour north of Los Angeles. Malpractice paid in full. This is a rare opportunity to combine a very attractive life-style with an excellent salary and benefit package. Call George Johnston, (805) 845-3731 for details or write Clinica Sierra Vista, PO Box 457, Lamont, CA 93241.

MEDICAL DIRECTOR. Community health clinic is seeking a Family Practice Physician to be responsible for the overall functioning of our medical program at our six clinics. Position is at our main clinic near Bakersfield in central California. Should be licensed to practice medicine in California and have proven clinical and administrative skills. Contact Stephen W. Schilling, Executive Director, Clinica Sierra Vista, PO Box 457, Lamont, CA 93241; (805) 845-3731.

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128.

SAN FRANCISCO BAY AREA. Large multispecialty, multi-facility group practice is seeking a BC/BE physician to join their expanding Occupational Medicine Department. Range of practice includes pre-employment physicals, diagnostic evaluations; treatment of on-the-job injuries. Competitive salary, excellent benefits and incentive plan, paid malpractice. Located in the South Bay which offers many cultural facilities, recreational activities, fine dining, outstanding scenery and climate, and easy access to San Francisco, Monterey, and the Sierra Nevada. For further information, please send CV or contact Maureen Forrester, Physician Recruitment, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

BC/BE FAMILY PRACTICE PHYSICIAN wanted to join five physician multispecialty group (three Family Practitioners, one General Surgeon, and one Internist) in northern California. Two and a half hours from San Francisco, two hours from Lake Tahoe, one hour from Sacramento. Contact C. J. Shieh, MD, 225 Spruce St, Gridley, CA 95948; (916) 846-5655.

MONTEREY PENINSULA, CALIFORNIA. BC/BE General Internist to join four other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established clinic practice. Excellent office, lab, x-ray department. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

TWO OB/GYNs to practice in "Wine Country" in Lake County, California. Located in a prime northern California resort area, within easy reach of San Francisco, with two hospitals and ample opportunity to build private practice. Assistance is available for relocation and practice establishment. Please contact the Administrator at Redbud Community Hospital, (707) 994-6486, or Lakeside Community Hospital, (707) 263-5651.

SAN FRANCISCO. Temporary full- and part-time positions available beginning June 15 for physicians BC/BE in Emergency Medicine, Internal Medicine, or Family Practice. Admitting Physician to provide inpatient care only; 24 hour shifts; acute care hospital in San Francisco; no call required; paid malpractice. Send CV to Chase Dennis Group, 400 Taylor Blvd, Ste 330, Pleasant Hill, CA 94523; (415) 676-2555.

(Continued on Page 618)

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PHYSICIANS WANTED

SAN DIEGO STATE UNIVERSITY STUDENT HEALTH SERVICES PHYSICIAN II

Ten month position. BC required. Family Practice strongly preferred. Salary range $5,488 to $6,642. EOE/AA/Title IX Employer. Interested candidates submit CV and letter to **Kevin Patrick, MD, Director, Student Health Services, San Diego State University, San Diego, CA 92182.**

ASSISTANT MEDICAL DIRECTOR, PHOENIX, ARIZONA. Maricopa County Health Plan, an expanding managed care organization with 40,000 current enrollees affiliated with Maricopa County Department of Health Services, seeks highly qualified physician for half-time clinical, half-time management position. Candidate should be BC in a primary care specialty with managed care experience and interest in indigent health care. Responsibilities include developing utilization review program, quality assurance, and ongoing direction of medical services. Competitive compensation package. Send CV to Gary Yates, MD, 400 N. 7th St, Ste 203, Phoenix, AZ 85006.

INTERNIST seeks BC/BE partner for historic rural area. Bustling practice with limitless opportunity serving Washington state island community. Safe and scenic. Convenient tertiary centers for referral and CME. Full service local hospital. Send résumé to PO Box 840, Coupeville, WA 98239.

INTERNAL MEDICINE, NORTHERN CALIFORNIA. You have a unique opportunity to join the area's leading multispecialty private medical practice. A position is available immediately for a BE/BC Internist. All subspecialties welcome to apply. Generous salary, bonus provision, fringe benefit package, and early membership in the corporation. Accept the challenge; become part of our competitive, growing organization. Experience the good life—wonderful restaurants, beautiful scenery, great weather, cultural facilities, easy access to beaches and mountains. Send CV and receive further information by contacting Christy Jensen or Maureen Forrester, Physician Recruitment, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833, (408) 282-7757.

NEUROLOGIST
for Full-Time Position in San Francisco Bay Area

Nation's largest HMO Kaiser Permanente seeks BE/BC Neurologist for immediate opening. EEG experience necessary; EMG a plus. Resident teaching opportunities. Academic affiliations encouraged. Competitive compensation and outstanding benefits including paid vacation, continuing education, life/medical/dental insurance, professional liability, retirement plans and full shareholdership within three years with profit-sharing. Send CV to:

Joel Richmon, MD
Dept of Neurology
Kaiser Permanente Medical Center
280 W. MacArthur Blvd
Oakland, CA 94611
Phone: (415) 596-6511

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

BC/BE RADIOLOGIST needed on Emerald Island of Kodiak, Alaska. Solo position utilizing five major referral sources on island, and some interaction with Radiology group in Anchorage. Population of 15,000 located on southern coast next to Aleutian Islands with moderate temperatures. Enjoy world's best fishing, hunting, and outdoor beauty, along with a strong economy. Financial package includes $150,000 income guarantee, all benefits, insurance, expenses, and relocation costs. Contact Paul Clukies, Jackson and Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

MEDICAL ONCOLOGIST BC/BE to join expanding 32 physician multispecialty group practice located in the foothills of the Blue Mountains in the state of Washington. The clinic serves a population area of 150,000. Full range of Radiation Oncology services are available in the community. Excellent schools, cultural and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE. Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

UROLOGIST, southern California. Urology group seeking new highly qualified BC partner. Ability in all radical surgery, ESWL, Endourology, prostheses, etc desired. Excellent smog-free coastal locale. Busy, expandable practice. Send CV to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PACIFIC NORTHWEST. General Internist, BC/BE, to join six Internists in small town 45 minutes from international airport. Beautiful setting; wet winter/spring, dry summer/fall. Guaranteed competitive salary/benefits; partnership option. Share call. Reply to Number 154, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

BE/BC RADIOLOGIST needed to join seven member Radiology group in upper midwestern community of 50,000. Strong professional opportunity with two hospitals including MRI, CT, colorflow, nuclear medicine, angiography, radial therapy, linear accelerator, etc. Excellent quality of life includes extensive vacation schedule, top level schools, a four year college, 40 hour week plus one in seven call/coverage. $150,000 salary with all benefits, insurance, malpractice, and relocation expenses. General diagnostic radiology position, MRI, and interventional experience desired. Contact Paul Clukies, Jackson and Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

PHYSICIANS WANTED

INTERNISTS

Practice in beautiful

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Hospital-based internists immediately needed at prestigious 132-bed Redding Medical Center. Large open-heart surgery program. Practice limited to inpatient general med. Xlent benefits (CME, vacation), min. guarantee of $125,000 annual take-home pay, plus FFS incentives, paid malpractice, and hospital provides billing. Flexible rotating call schedule. Incredible opportunity!

Hospital lies in the shadow of Mt. Shasta. Great recreational and family area. Contact:

Gary L. Groves, MD
(714) 825-4401 in CA
or (800) 338-4798

PHYSICIANS WHO ARE BC/BE in Family Practice/Internal Medicine with emergency room experience are being sought for full-time/part-time positions in the urgent care department of a multispecialty group. Primarily ambulatory care with occasional emergency room shifts. No on-call responsibilities. Generous compensation and benefits, including partnership opportunity. Send CV to Daniel Polite, MD, Urgent Care Dept, The Permanente Medical Group, Inc, 770 E. Calaveras Blvd, Milpitas, CA 95035.

INFECTIOUS DISEASE. Dynamic hospital based Internal Medicine/Pulmonary four man group seeks BE/BC Infectious Disease associate. Some critical care skills required. Beautiful waterfront community near Seattle. Outstanding financial package. Send CV to Number 155, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WANTED BC/BE PEDIATRICIANS

Nighttime pediatrics clinic. For information see article in *Contemporary Peds,* July 1987. Part-/full-time 20 to 40 hours per week. Salary negotiable. Inquire c/o

Jed Dunford
279 East 5900 South
Murray, UT 84107

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PHYSICIANS WANTED

FAMILY PRACTICE/URGENT CARE—IMMEDIATE OPPORTUNITIES

for BC/BE physicians in northern and central California. Excellent salary compensations and benefits. Also private practices available in Sacramento, Modesto-Stockton area, and Contra Costa County. Please send CV or call **Mary Frances Malone, Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.**

INSTITUTION PHYSICIAN NEEDED to staff the Wyoming State Training School in Lander, Wyoming. We have 360 clients in an institutional setting for acute care in an 18 bed health care center. There is a staff of three physicians and one Physician's Assistant for total medical services. Salary commences at $55,326 per year. Attractive benefits, no overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Hwy 789, Lander, WY 82520; (307) 332-5302. An Equal Opportunity Employer.

INTERNAL MEDICINE. Kaiser Permanente office in central California, rapidly growing new market area, seeking BC/BE physicians in the Department of Medicine. Address inquiries to Antonis Antoniou, MD, Assistant Physician-in-Charge, Kaiser Permanente, 4785 N. First St, Fourth Floor, Fresno, CA 93726; (209) 221-4944.

WASHINGTON. General Internist BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is composed of 32 physician multispecialty group. Guaranteed income, plus excellent benefits. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

FAMILY PRACTICE OPPORTUNITY. Association available in rural town one hour from Seattle and one-half hour from Tacoma. Obstetrics optional. Growing community close to mountains and Puget Sound. Owner to retire in four to five years. Reply to Number 156, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

FACULTY POSITION available July 1, 1989, in community-based University of Washington Family Practice residency in beautiful Pacific northwest. Responsibilities to include patient care, resident teaching and supervision, and limited program administration. Obstetrics required. Salary and benefits based on experience. Direct CV and inquiries to Philip D. Cleveland, MD, Director, Family Medicine Spokane, S. 510 Cowley, Spokane, WA 99202; (509) 624-2313.

ROSEVILLE. Immediate opening for BC/BE Family Practitioner. Ours is a satellite clinic in a group model HMO. Practice is primarily adult care with no OB or night call. Attractive salary, comprehensive benefit package, opportunity for shareholder status available. Malpractice provided. Contact Richard Fury, MD, The Permanente Medical Group, Inc, 1001 Riverside Ave, Roseville, CA 95678; (916) 784-4620.

FAMILY PRACTICE/INTERNAL MEDICINE/OB/GYN

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(Continued on Page 620)

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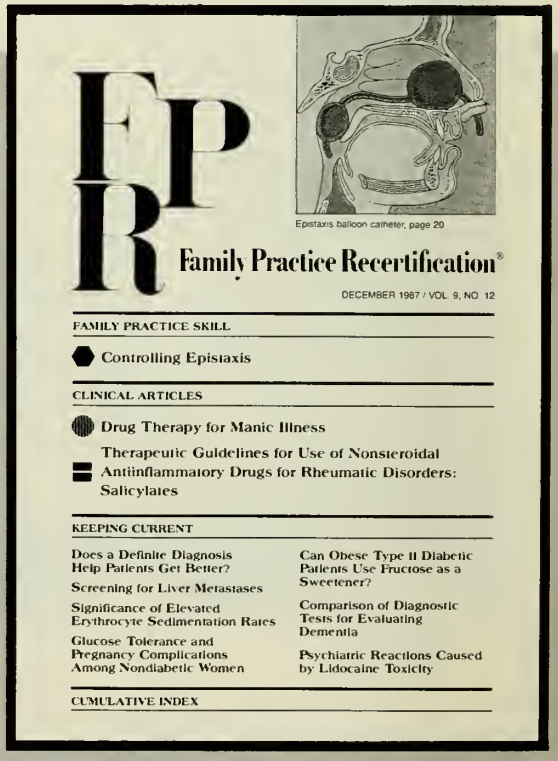

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 1-3, 1989, Pointe at South Mountain, Phoenix.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 14-17, 1989, Westin Hotel, Vail.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-29, 1989, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

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New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-13, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 13-15, 1989, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 28-October 1, 1989, SEATAC Red Lion, Seattle.

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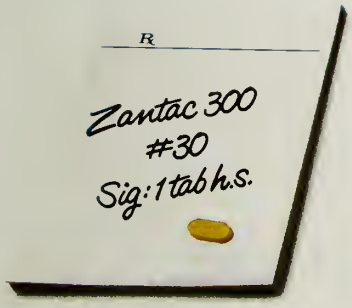

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

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The portrait of anxiety

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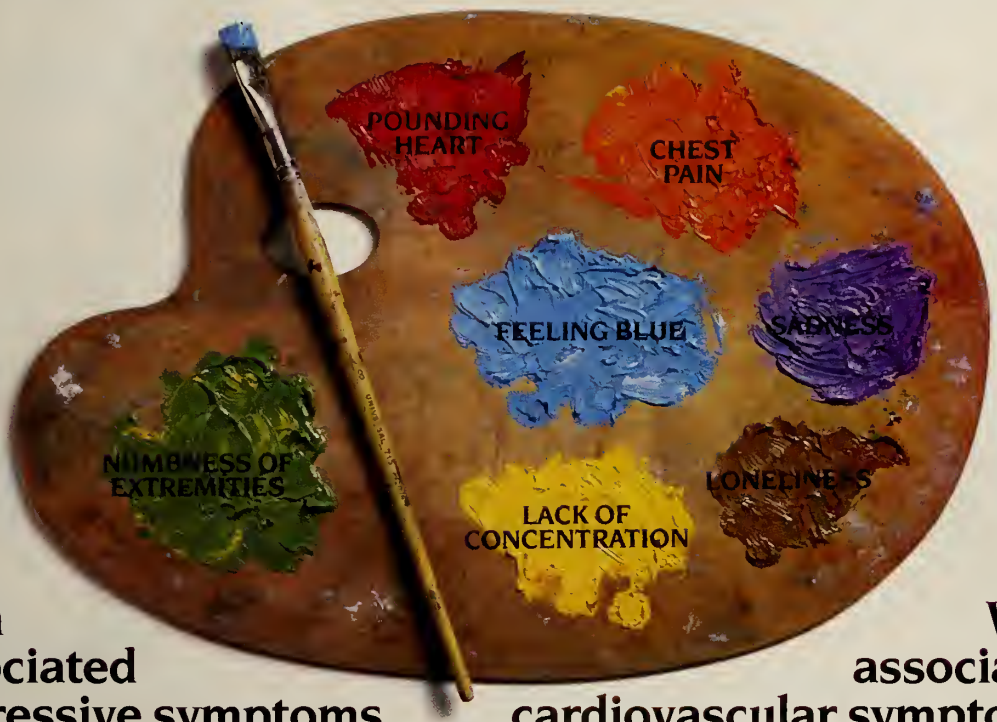
is often complicated



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In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

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- *Simple dosage*—0.25 to 0.5 mg t.i.d.

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for the relief of complicated anxiety

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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
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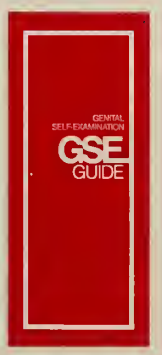

The GSE is the heart of a nationwide campaign to heighten public awareness of STDs. This program is sponsored by Burroughs Wellcome Co. in conjunction with major medical associations.*

Sexually active adults will be urged to send for a free guide that explains how to perform a GSE. The guide discourages self-diagnosis and encourages seeing a physician if anything suspect is found.

As the GSE campaign gains momentum, you may be seeing more patients coming to your office with concerns about sexually transmitted diseases. While STDs are currently regaining their foothold on the American population, the GSE program offers a promising outlook for reducing their spread.

*The American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, and the American Osteopathic Association.

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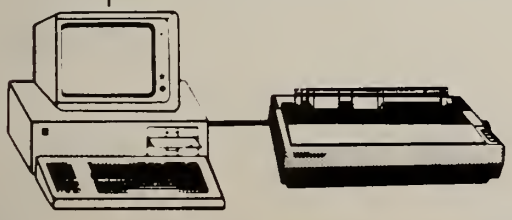

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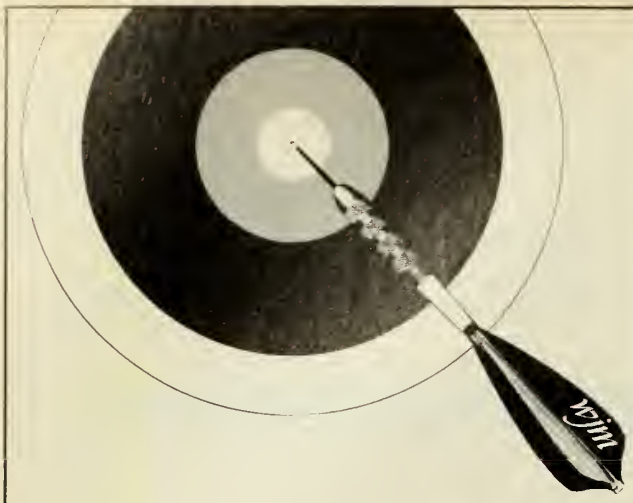

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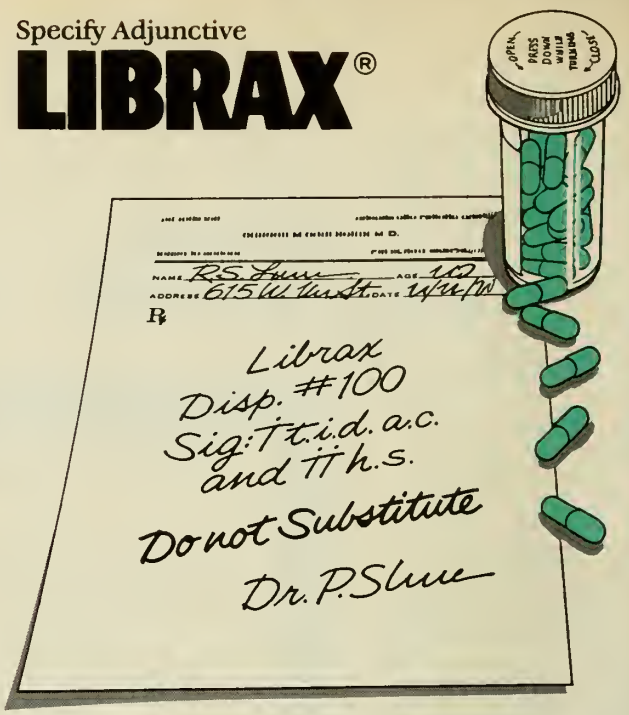

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Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

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Manati, Puerto Rico 00701

Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

In IBS,* when it's brain versus bowel,

IT'S TIME FOR THE PEACEMAKER.

In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

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Please see summary of prescribing information on adjacent page.

Placebo-like side effect profile at the 1 mg dose

Real-life benefits with TENEX® (Guanfacine HCl)

1 mg Tablets

When more than a thiazide diuretic is needed

A·H·ROBINS

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: ***General.*** Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n=	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n=279)	Clonidine (n=278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweeting
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n=20), weakness (n=12), constipation (n=7), somnolence (n=3), nausea (n=3), orthostatic hypotension (n=2), insomnia (n=1), rash (n=1), nightmares (n=1), headache (n=1), and depression (n=1).

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Reasons To Choose Clinoril® First

TABLETS, 150 mg and 200 mg

(Sulindac|MSD)

NOW AVAILABLE ON MEDI-CAL

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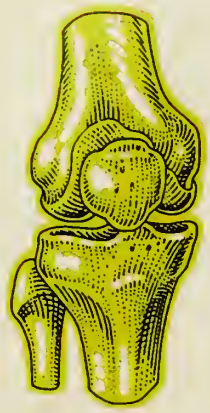
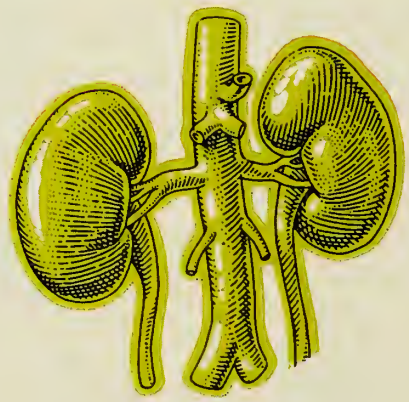
CLINORIL, 200-mg tablet—2048B



Prompt relief of the signs and symptoms of osteoarthritis. CLINORIL at 200 to 400 mg daily was comparable in effectiveness to aspirin 2400 to 4800 mg daily.

CLINORIL is contraindicated in patients who are hypersensitive to this product or in whom acute asthmatic attacks, urticaria, or rhinitis is precipitated by aspirin or other NSAIDs.

Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.



CLINORIL may affect renal function to a lesser extent than other NSAIDs;* however, renal adverse effects have been reported.

Caution should be exercised when administering CLINORIL to patients with conditions associated with increased risk of the effects of NSAIDs on renal function, such as those with complications associated with advanced age.

*These observations need further clarification, and, in the interim, CLINORIL should be used with caution in patients whose renal function may be impaired or prostaglandin dependent or who have a history of renal lithiasis. Such patients should be closely monitored.

No reported blunting of certain antihypertensive agents.

Edema has been observed in some patients taking CLINORIL. Therefore, as with other NSAIDs, CLINORIL should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

For a Brief Summary of Prescribing Information, please see the following page.

MSD
MERCK SHARP & DOHME

For many osteoarthritic patients age 65 and older

Choose Clinoril® First

TABLETS 150 mg and 200 mg

(Sulindac | MSD)

Contraindications: Hypersensitivity to this product; patients in whom acute asthmatic attacks, urticaria, or rhinitis is precipitated by aspirin or other nonsteroidal anti-inflammatory agents.

Warnings: *Gastrointestinal Effects:* Peptic ulceration and gastrointestinal bleeding have been reported. Fatalities have occurred. Gastrointestinal bleeding is associated with higher morbidity and mortality in patients acutely ill with other conditions, the elderly, and patients with hemorrhagic disorders. In patients with active gastrointestinal bleeding or an active peptic ulcer, an appropriate ulcer regimen should be instituted, benefits of therapy must be weighed against possible hazards, and the patient's progress carefully monitored; in patients with a history of either upper or lower gastrointestinal tract disease, CLINORIL® (Sulindac, MSD) should be given under close supervision and only after consulting the ADVERSE REACTIONS section.

Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Hypersensitivity: Rarely, fever and other evidence of hypersensitivity (see ADVERSE REACTIONS), including abnormalities in one or more liver function tests and severe skin reactions, have occurred; fatalities have occurred in these patients. Hepatitis, jaundice, or both, with or without fever, may occur usually within the first one to three months of therapy. Determinations of liver function should be considered whenever unexplained fever, rash or other dermatologic reactions, or constitutional symptoms develop; if unexplained fever or other evidence of hypersensitivity occurs, discontinue CLINORIL. Elevated temperature and abnormalities in liver function caused by CLINORIL characteristically have reverted to normal after discontinuation of therapy. CLINORIL should not be reinstituted in such patients.

Hepatic Effects: In addition to hypersensitivity reactions involving the liver, in some patients the findings are consistent with those of cholestatic hepatitis. As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests without any other signs and symptoms may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with CLINORIL. Although such reactions as described above are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CLINORIL should be discontinued. In clinical trials, the use of 600 mg/day has been associated with increased incidence of mild liver test abnormalities (maximum recommended dosage is 400 mg per day).

Precautions: *General:* Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS: *Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy*). Although the effect on platelet function and bleeding time is less than with aspirin, CLINORIL is an inhibitor of platelet function; therefore, patients who may be adversely affected should be carefully observed when CLINDRIL is administered. Pancreatitis has been reported (see ADVERSE REACTIONS); should pancreatitis be suspected, the drug should be discontinued and not restarted, supportive medical therapy instituted, and the patient monitored closely with appropriate laboratory studies (e.g., serum and urine amylase, amylase/creatinine clearance ratio, electrolytes, serum calcium, glucose, lipase, etc.); a search for other causes of pancreatitis as well as those conditions which mimic pancreatitis should be conducted. Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop eye complaints during treatment have ophthalmologic studies. In patients with poor liver function, delayed, elevated and prolonged circulating levels of the sulfide and sulfone metabolites may occur. Such patients should be monitored closely; a reduction of daily dosage may be required.

Edema has been observed in some patients taking CLINORIL. Therefore, as with other nonsteroidal anti-inflammatory drugs, CLINORIL should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention. CLINDRIL may allow a reduction in dosage or the elimination of chronic corticosteroid therapy in some patients with rheumatoid arthritis. However, it is generally necessary to reduce corticosteroids gradually over several months in order to avoid an exacerbation of disease or signs and symptoms of adrenal insufficiency. Abrupt withdrawal of chronic corticosteroid treatment is generally not recommended even when patients have had a serious complication of chronic corticosteroid therapy.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of sulindac to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, the administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. CLINDRIL may affect renal function less than other NSAIDs in patients with chronic glomerular renal disease (see CLINICAL PHARMACOLOGY section of Prescribing Information). Until these observations are better understood and clarified, however, and because renal adverse experiences have been reported with CLINDRIL (see ADVERSE REACTIONS), caution should be exercised when administering the drug to patients with conditions associated with increased risk of the effects of nonsteroidal anti-inflammatory drugs on renal function, such as those with renal or hepatic dysfunction, diabetes mellitus, complications associated with advanced age, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. Since sulindac is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation. Since sulindac metabolites have been reported rarely as a component of renal stones, patients with a history of renal lithiasis should be given CLINDRIL® (Sulindac, MSD) with caution and be kept well hydrated.

Information for Patients: CLINORIL, like other drugs of its class, is not free of side effects and can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis but also may be commonly employed for less serious conditions. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIDNS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly in less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Use in Pregnancy: Not recommended for use in pregnant women, since safety for use has not been established and because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus) during the third trimester of pregnancy.

Nursing Mothers: Nursing should not be undertaken while a patient is on CLINORIL. It is not known whether sulindac is secreted in human milk; however, it is secreted in the milk of lactating rats.

Use in Children: Safety and effectiveness in children have not been established.

Drug Interactions: DMSD should not be used with sulindac; concomitant administration has been reported to reduce plasma levels of active sulfide metabolite and potentially reduce efficacy and to cause peripheral neuropathy. Although sulindac and its sulfide metabolite are highly bound to protein, studies with daily doses of 400 mg have shown no clinically significant interaction with oral anticoagulants or oral hypoglycemic agents; however, patients should be monitored carefully until it is certain that no change in their anticoagulant or hypoglycemic dosage is required. Special attention should be paid to patients taking higher doses than those recommended and to patients with renal impairment or other metabolic defects that might increase sulindac blood levels. Concomitant administration of aspirin significantly depressed the plasma levels of the active sulfide metabolite. Although addition of aspirin did not alter the types of clinical or laboratory adverse experiences, the combination showed an increase in the incidence of gastrointestinal adverse experiences; since addition of aspirin did not have a favorable therapeutic effect, the combination is not recommended. Concomitant administration of diflunisal in normal volunteers resulted in lowering of plasma levels of active sulindac sulfide metabolite by approximately one-third. Probenecid given concomitantly had only a slight effect on plasma sulfide levels, while plasma levels of sulindac and sulfone were increased; sulindac produced a modest reduction in the uricosuric action of probenecid, which probably is not significant under most circumstances. Neither propoxyphene hydrochloride nor acetaminophen had any effect on the plasma levels of sulindac or its sulfide metabolite.

Adverse Reactions: The following adverse reactions were reported in clinical trials or have been reported since the drug was marketed. The probability exists of a causal relationship between CLINORIL and these adverse reactions. The adverse reactions which have been observed in clinical trials encompass observations in 1,865 patients, including 232 observed for at least 48 weeks.

Incidence Greater than 1%: Gastrointestinal—Gastrointestinal pain (10%), dyspepsia,* nausea* with or without vomiting, diarrhea,* constipation,* flatulence, anorexia, gastrointestinal cramps. *Dermatologic*—Rash,* pruritus. *Central Nervous System*—Dizziness,* headache,* nervousness. *Special Senses*—Tinnitus. *Miscellaneous*—Edema (see PRECAUTIDNS).

Incidence Less than 1%: Gastrointestinal—Gastritis, gastroenteritis, or colitis; peptic ulcer; gastrointestinal bleeding; GI perforation; liver function abnormalities; jaundice, sometimes with fever; cholestasis; hepatitis; pancreatitis (see PRECAUTIONS); ageusia; glossitis; a single report of sulindac metabolites in common bile duct "sludge" in a patient with symptoms of cholecystitis who underwent a cholecystectomy. *Dermatologic*—Stomatitis, sore or dry mucous membranes, alopecia, photosensitivity, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis. *Cardiovascular*—Congestive heart failure, especially in patients with marginal cardiac function; palpitation; hypertension. *Hematologic*—Thrombocytopenia; ecchymosis; purpura; leukopenia; agranulocytosis; neutropenia; bone marrow depression, including aplastic anemia; hemolytic anemia; increased prothrombin time in patients on oral anticoagulants (see PRECAUTIONS). *Genitourinary*—Urine discoloration; vaginal bleeding; hematuria; proteinuria; crystalluria; renal impairment, including renal failure; interstitial nephritis; nephrotic syndrome; renal calculi containing sulindac metabolites have been observed rarely. *Metabolic*—Hyperkalemia. *Psychiatric*—Depression; psychic disturbances, including acute psychosis. *Nervous System*—Vertigo, insomnia, somnolence, paresthesia, convulsions, syncope, aseptic meningitis. *Special Senses*—Blurred vision, visual disturbances, decreased hearing, metallic or bitter taste. *Respiratory*—Epistaxis. *Hypersensitivity Reactions*—Anaphylaxis, angioneurotic edema, bronchial spasm, dyspnea, hypersensitivity vasculitis. A potentially fatal apparent hypersensitivity syndrome has been reported; this syndrome may include constitutional symptoms (fever, chills), cutaneous findings (rash or other dermatologic reactions—see above), involvement of major organs (changes in liver function, jaundice, pancreatitis, pneumonitis with or without pleural effusion, leukopenia, eosinophilia, disseminated intravascular coagulation, anemia, renal impairment, including renal failure), and other less specific findings (adenitis, arthralgia, myalgia, fatigue, malaise, hypotension, chest pain, tachycardia).

Causal Relationship Unknown: Other reactions have been reported in clinical trials or since the drug was marketed but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians. *Cardiovascular*—Arrhythmia. *Metabolic*—Hyperglycemia. *Nervous System*—Neuritis. *Special Senses*—Disturbances of the retina and its vasculature. *Miscellaneous*—Gynecomastia.

Dosage and Administration: CLINORIL should be administered orally twice a day with food. The maximum dosage is 400 mg per day; dosages above 400 mg per day are not recommended. In osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, the recommended starting dosage is 150 mg twice a day; the dosage may be lowered or raised depending on the response. A prompt response (within one week) can be expected in about one half of patients with osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis; others may require longer to respond. In acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis) and acute gouty arthritis, the recommended dosage is 200 mg twice a day; after a satisfactory response has been achieved, the dosage may be reduced according to the response. In acute painful shoulder, therapy for 7-14 days is usually adequate. In acute gouty arthritis, therapy for 7 days is usually adequate.

Management of Overdosage: Overdosage has been reported, and rarely deaths have occurred. In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Animal studies show that absorption is decreased by the prompt administration of activated charcoal and excretion is enhanced by alkalinization of the urine.

How Supplied: Tablets CLINDRIL containing 150 mg or 200 mg sulindac, with cellulose, magnesium stearate, and starch as inactive ingredients, in unit-of-use bottles of 60 and 100, unit-dose packages of 100, and bottles of 100.

*Incidence between 3% and 9%. (Those reactions occurring in less than 3% of patients are unmarked.)

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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Once-A-Day

Vaseretic®

(Enalapril Maleate-Hydrochlorothiazide|MSD)

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: ***Hypotension:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia. Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension — Patients on Diuretic Therapy.* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release.* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents.* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium.* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium.* See WARNINGS, *Hydrochlorothiazide*, and PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide.*

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics. *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs* — additive effect or potentiation. *Corticosteroids, ACTH* — intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)* — possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)* — possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk, however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Cardiovascular:* Syncope, orthostatic hypotension, palpitations, chest pain, tachycardia. *Gastrointestinal System.* Abdominal pain, vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous System:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, pruritus, decreased libido, rash, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension.* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN:* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*). *Gastrointestinal System.* Ileus, pancreatitis, hepatitis or cholestatic jaundice. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, rhinorrhea. *Other:* Photosensitivity, alopecia, flushing, taste alteration, glossitis. A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide — Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 3418—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

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ARIZONA

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 28-29—**Coconino County Medical Society Summer Seminar and Day of Surgery.** Little America, Flagstaff. Fri-Sat. Contact: Coconino County Medical Society, PO Box 392, Flagstaff 86002.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

July 21-22—**American In-Vitro Allergy/Immunology Society Annual Program.** American In-Vitro Allergy/Immunology Society at San Diego Marriott Hotel and Marina. Fri-Sat. 12 hrs. $200. Contact: Betty Kahler, PO Box 459, Lake Jackson, TX 77566. (409) 297-5636.

September 21-22—**Modern Approaches to Allergy and Clinical Immunology.** UCSF at Hyatt Union Square, San Francisco. Thurs-Fri. 15 hrs. $300. Contact: UCSF.

ANESTHESIOLOGY

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 17 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $100. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 22-24—**Anesthesia Practice 1989.** Anesthesiology Educational Foundation at Hyatt Regency, Monterey. Fri-Sun. 12.5 hrs. Contact: AEF, PO Box 24230, Los Angeles 90024. (213) 825-0736.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 17-19—**UCD Anesthesiology Update.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

CARDIOLOGY

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 23-24—**Advanced Cardiac Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 642)

(Continued from Page 641)

June 24—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

July 15—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: Deborah Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

September 20—**Optimum Use of Diagnostic and Therapeutic Technologies in Clinical Practice.** American Heart Association Los Angeles at Beverly Hilton. Wed. 9 hrs. $120. Contact: Marlin Ledbetter, 3550 Wilshire Blvd, Ste 500, Los Angeles 90010. (213) 385-4231.

DERMATOLOGY

June 25—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 16—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

June 23-24—**Advanced Cardiac Life Support.** Center for Health Education at Long Beach. Fri-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 24-25—**11th Annual Poison Center Symposium: Emergency Medicine and Toxicology.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $280. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 19-22—**Traumatic Brain Injury.** UCD at Hyatt Regency, Sacramento. Thurs-Sun. 27 hrs. Contact: UCD.

INTERNAL MEDICINE

June—**Seminars in Cytopathology 1989.** UCSF at Health Sciences Room 300. Thurs/monthly. 12 hrs. $140 full series/$30 single. Contact: UCSF.

June 14-16—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at The Portman Hotel. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 30-July 2—**California Society of Internal Medicine: 44th Annual Meeting.** California Society of Internal Medicine at Maui Marriott Hotel, Kaanapali Beach. Fri-Sun. 4 hrs. $125. Contact: Cynthia Eaton, PO Box 880606, San Francisco 94188-0606. (415) 882-5198.

August 20-25—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

September 4-5—**International Conference on Thyroid Metabolism.** UCI at Queen Mary Hotel, Long Beach. Mon-Tues. Contact: UCI.

September 7-9—**New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Shirley Kolkey, PO Box 210211, San Diego 92121. (619) 453-6222.

(Continued on Page 644)

EMC*Express™ submits claims to these insurance carriers:

ARIZONA Aetna-Medicare Part B
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NEVADA Aetna-Medicare Part B
NEW MEXICO Aetna-Medicare Part B
WASHINGTON Blue Cross and Blue Shield of Washington/Alaska-Medicare Part B (Development)
WYOMING Equitable-Medicare Part B

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The New England
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The following vendors have incorporated the EMC*Express™ system into their physician practice management software:

SYSTEM VENDORS

Advanced Medical Office Systems (AMOS)	209-466-1807
Alcon	1-800-225-5489
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Artificial Intelligence	1-800-533-8902
The Cactus Medical Group, Ltd.	1-800-876-9495
CYMA/McGraw Hill	1-800-292-2962
GSR Systems, Inc.	1-800-426-9478
Healthcare Communications	402-489-0391
LDS	913-492-5700
Mid-Atlantic ICS, Inc.	1-800-772-2842
MOS, Inc.	1-800-323-6671
The Oakmark Corporation	619-268-7632
Physician Micro Systems	206-441-8490
Physicians' Office Computer	213-603-0555
PRISM Data Systems	1-800-223-3828
ProVision, Inc.	1-800-772-2847
RLI Professional Technologies, Inc.	1-800-447-2205
Santiago Data Systems, Inc.	1-800-652-3500
UNIVAIR, Inc.	314-426-1099
Westland Software House, Inc.	1-800-423-5880

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CONTINUING MEDICAL EDUCATION

(Continued from Page 642)

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

November 2-4—**San Francisco Otology Update: 1989.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 22 hrs. $385. Contact: UCSF.

November 3-5—**Bone and Soft Tissue Tumors Diagnostic Imaging Modalities, Pathology and Treatment.** UCD at Sheraton Sunrise, Sacramento. Fri-Sun. Contact: UCD.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

OB/GYN

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

June 30-July 4—**7th Annual Controversies in OB/GYN.** UCI at Mauna Kea, Hawaii. Fri-Tues. Contact: UCI.

July 29-August 8—**Update in Urogynecology.** UCI at Hawaii. 1 week/2 days. Contact: UCI.

October 12-13—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott Hotel, Newport Beach. Thurs-Fri. Contact: UCI.

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

OPHTHALMOLOGY

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

September 15-16—**Uveitis Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Quail Lodge, Carmel Valley. Fri-Sat. Contact: UCSF.

PEDIATRICS

June 16-17—**Current Concepts in Pediatric Respiratory Disease.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Fri-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

June 23-24—**Breastfeeding for Health Professionals.** UCSF at Hyatt Oakland International Airport. Fri-Sat. 10 hrs. $75. Contact: UCSF.

July 10-12—**Seminar for Physicians: Breastfeeding: A Natural World Resource.** La Leche League International at Anaheim Hilton and Towers. Mon-Wed. 16 hrs. Contact: LLLI, 9616 Minneapolis Ave, Franklin Park, IL 60131. (312) 455-7730.

(Continued on Page 653)

Professional Use Information

CARAFATE®
(sucralfate) Tablets

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours This interaction appears to be non-systemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose) There was no evidence of drug-related tumorgenicity A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted

Pregnancy: Teratogenic effects Pregnancy Category B Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4 7%).

Constipation was the most frequent complaint (2.2%) Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo

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Please see brief summary of prescribing information on adjacent page.

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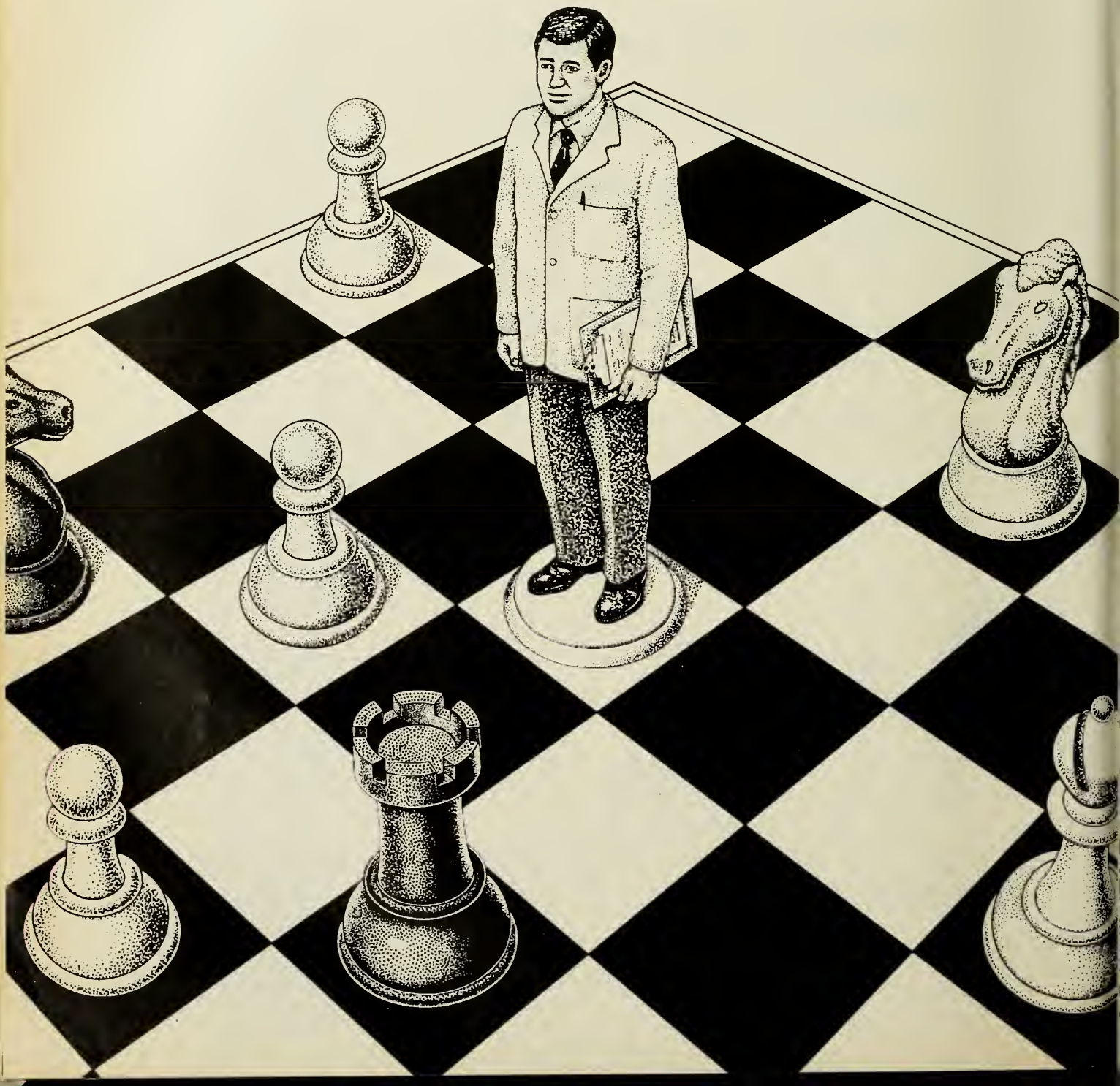

In Memoriam

Arizona Medical Association

AHL, CARL W., Douglas. Died Mar 30, 1989, aged 89. Graduate of University of Minnesota Medical School, Minneapolis, 1938. Licensed in Arizona in 1950. Dr Ahl was a member of the Cochise County Medical Society.

❧

CHERMAK, FRANCIS G., Phoenix. Died Jan 14, 1989, aged 80. Graduate of University of Minnesota Medical School, Minneapolis, 1937. Licensed in Arizona in 1964. Dr Chermak was a member of the Maricopa County Medical Society.

❧

DAVIDSON, JUDSON A., Phoenix. Died Nov 6, 1988, aged 58. Graduate of Vanderbilt University School of Medicine, Nashville, 1956. Licensed in Arizona in 1963. Dr Davidson was a member of the Maricopa County Medical Society.

❧

EBALO, MARCIAL M., Scottsdale. Died Jan 23, 1989, aged 56. Graduate of University of Philippines, Manila, 1958. Licensed in Arizona in 1970. Dr Ebalo was a member of the Maricopa County Medical Society.

❧

KOSSUTH, LOUIS C., Phoenix. Died Apr 15, 1989, aged 75. Graduate of Case Western Reserve University School of Medicine, Cleveland, 1939. Licensed in Arizona in 1949. Dr Kossuth was a member of the Maricopa County Medical Society.

❧

MARLOWE, WILLIAM H., Prescott. Died Mar 28, 1989, aged 73. Graduate of Northwestern University Medical School, Chicago, 1942. Licensed in Arizona in 1954. Dr Marlowe was a member of the Yavapai County Medical Society.

❧

ROTH, MONTY, Tempe. Died Jan 11, 1989, aged 59. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1961. Licensed in Arizona in 1983. Dr Roth was a member of the Maricopa County Medical Society.

New Mexico Medical Society

KURTZ, CHESTER, Albuquerque. Died Feb 1989, aged 90. Graduate of Harvard School of Medicine, Boston, 1927. Licensed in New Mexico in 1966. Dr Kurtz was a member of the Greater Albuquerque Medical Association.

❧

PIJOAN, MICHAEL, Corrales. Died Feb 8, 1989, aged 80. Graduate of Johns Hopkins University, Baltimore, 1934. Licensed in New Mexico in 1951. Dr Pijoan was a member of the New Mexico Medical Society.

Utah Medical Association

ALSTON, ROBERT MOSS, Salt Lake City. Died Mar 20, 1989, aged 45. Graduate of University of Utah, 1969. Licensed in Utah in 1976. Dr Alston was a member of the Salt Lake County Medical Society.

❧

CALL, WILLIAM DEE, Salt Lake City. Died Nov 25, 1988, aged 66. Graduate of Temple University, Philadelphia, 1946. Licensed in Utah in 1952. Dr Call was a member of the Salt Lake County Medical Society.

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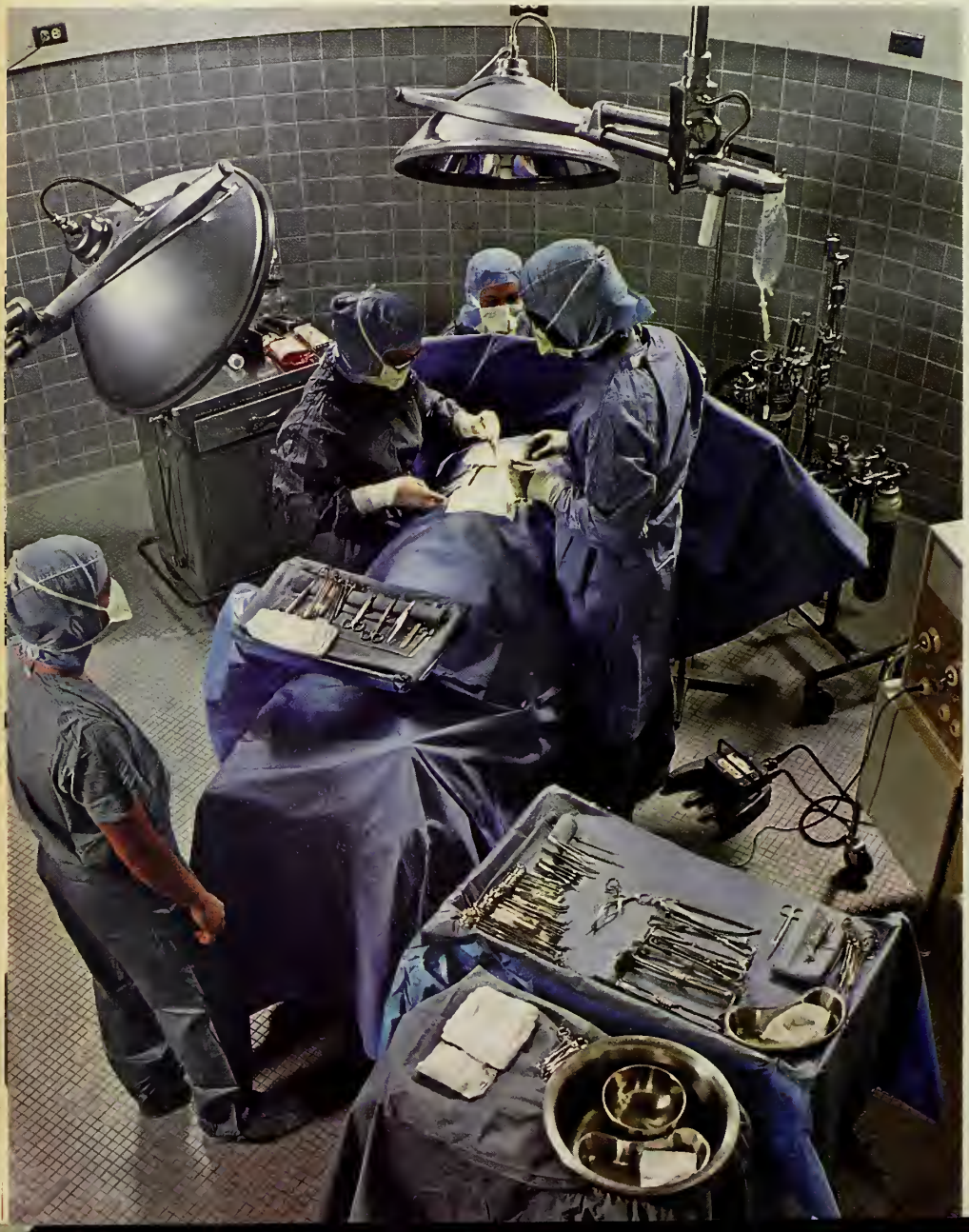

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Reference. 1. Data on file, Burroughs Wellcome Co.

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Please see brief summary of prescribing information on next page.

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Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤ 10 ml/min/1.73 m^2

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).

Store at 15°-30°C (59°-86°F) and protect from light and moisture.

U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials, in most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest, pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostate hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the liketihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium <130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J6VS18R(815)

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(Continued from Page 644)

July 18—**22nd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel Nob Hill, San Francisco. Thurs-Sat. 16 hrs. $275. Contact: UCSF.

July 21-22—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

August 11-13—**2nd Annual Postgraduate Course.** UCI at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

October 13-14—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

PSYCHIATRY

October 13-15—**California Psychiatric Association Annual Meeting** at Del Coronado Hotel, San Diego. Fri-Sun. Contact: Barbara Gard, 221 Main St, Ste 352, San Francisco 94105-9832. (415) 882-5196.

RADIOLOGY

July 27-30—**3rd Annual Symposium on Magnetic Resonance Imaging.** Ritz-Carleton Resort Hotel, Laguna Niguel. Thurs-Sun. 23 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 29—**Abdominal Imaging Conference.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

July 30-August 3—**Napa Valley Imaging Update: MRI 1989.** UCD at Silverado Country Club, Napa Valley. Sun-Thurs. 17 hrs. $435. Contact: Nina Musselman, (916) 453-5390.

July 31-August 4—**Modern Radiology Practice.** UCSD at Four Seasons Biltmore Hotel, Santa Barbara. Mon-Fri. 24 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 24-27—**Physics and Biology of Radiology.** UCSD at Town & Country Hotel, San Diego. Thurs-Sun. 25 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 7-10—**5th Annual Sonography Update for Physicians and Sonographers.** UCSD at San Diego Marriott Hotel and Marina. Thurs-Sun. 18 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 23-24—**Weekend MRI Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Sat-Sun. 12 hrs. $195. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

October 2-5—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center and University of Cincinnati College of Medicine at Ritz-Carlton Hotel, Laguna Niguel. Mon-Thurs. 18 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 7-8—**Ultrasound Update: 1989.** UCD at Red Lion Inn, Sacramento. Sat-Sun. Contact: UCD.

October 12-14—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center Cincinnati at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sat. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

(Continued on Page 657)

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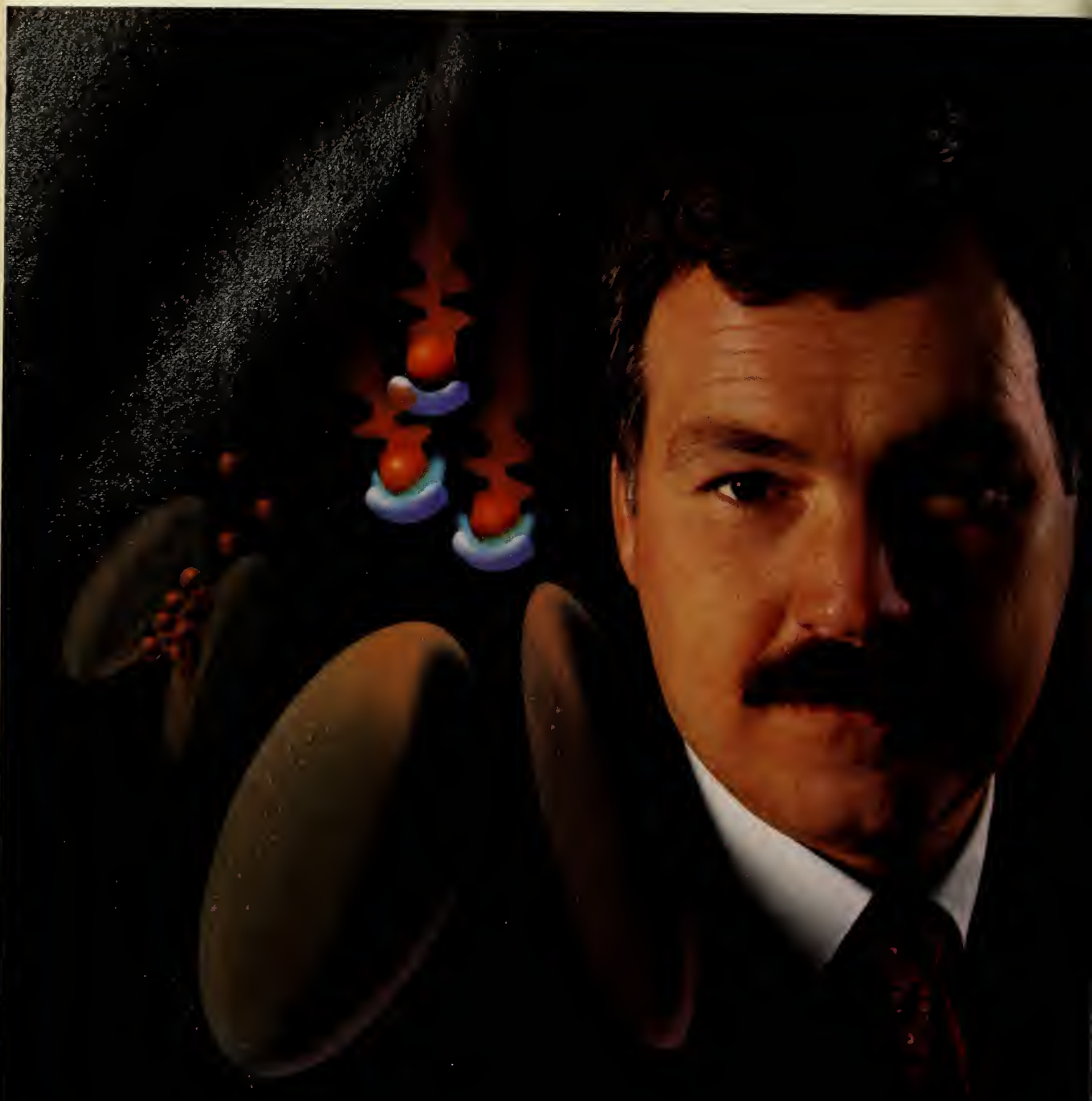

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Artist's visualization: blockade of the "anchor" proteins preventing platelet aggregation.

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"The pathophysiology of cardiovascular disease generally involves proteins not doing what they should."
"Either they're not doing their job, overdoing it, or doing something else that's not appropriate. If we are going to reverse fundamental disease processes, we will have to correct 'misbehavior' involving at least four different types of proteins: (1) 'operators'—the enzymes that actually perform the body's metabolic work; (2) 'anchors'—proteins that bind one cell to another; (3) 'triggers'—the receptor sites that initiate response machinery within a cell; and (4) 'conduits'—the channels that facilitate the entrance of specific types of ions into excitable tissue."

"'Operator' enzymes are primary factors in thromboembolic and hypertensive disease."
"A specific approach to these diseases could involve eliminating or inactivating an offending enzyme. By contrast, one could enhance a desirable enzymatic activity as with tissue plasminogen activator (t-PA). Now, with the aid of molecular biology, we are finding ways to modulate the expression and function of enzymes that are of key pathophysiological importance."

"Thromboembolism cannot occur without the 'anchor' proteins that bind platelets together."
"Activation of platelets exposes 'docking sites' for these anchor molecules to bind. Antiplatelet drugs work through only one of a myriad of mechanisms that can lead to platelet activation. But if one interferes with the binding of protein 'anchors' to their docking sites, platelets cannot aggregate to form thrombi no matter how they become activated."

"We need more specific blocking agents."
"Adrenergic receptor blockers inhibit a receptor site trigger that mediates a detrimental effect of epinephrine. But epinephrine is usually not a specific cause of disease—it merely exacerbates it. If one could identify a 'trigger' specifically related to the disease process, one might be able to eliminate it. Similar considerations apply to 'conduit' blockers. A familiar example is the therapeutic usefulness of calcium channel blockers. A more specific approach that targets an abnormal 'conduit' could be the key to preventing ventricular fibrillation and sudden cardiac death."

"We look for a common thread that allows us to interfere with a fundamental disease process."
"If there are multiple ways of activating a disease process, we are not going to control it by blocking just one. The disease will continue. But if one can find and block a common pathway, all of those mechanisms will be invalidated.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 653)

October 30-November 3—**14th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 3-5—**9th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

June-December—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

June 24—**7th Annual Prosthetics/Orthotics Course.** UCD at The Medical Center, Sacramento. Sat. Contact: UCD.

July 19-22—**5th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic and Research Foundation at La Jolla. Wed-Sat. 25 hrs. $799. Contact: Judy Plis, Scripps Clinic, La Jolla 92037. (619) 554-8646.

August 5-12—**Fine Needle Biopsy Course.** UCSF at Westin Hotel, Kauai, Hawaii. 1 week. 25 hrs. $895. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

September 15—**Ultrasonic Liver Surgery.** UCD at Davis. Fri. 8 hrs. $250. Contact: UCD.

October 11-14—**Hip and Knee Reconstructive Surgery 1989.** UCLA at Sheraton Kauai Hotel Poipu Beach, Kauai, Hawaii. Wed-Sat. Contact: UCLA. (213) 825-5840.

OF INTEREST TO ALL PHYSICIANS

June 11-16—**Family Practice Refresher Course.** UCI at Newport Beach Sheraton. Sun-Fri. 30 hrs. Contact: UCI.

June 11-16—**13th Annual Fingers to the Toes: Comprehensive and Practical Orthopaedics for Primary Care and Emergency Medicine Physicians.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 37 hrs. Contact: UCD.

June 19-23—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics, OB/GYN, ENT, Dermatology, Legal Aspects, Psychiatry, Ophthalmology, Toxicology, Oral Surgery, Pharmacology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 23—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 23-24—**Legal Aspects of Addiction Medicine.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Sir Francis Drake Hotel, San Francisco. Fri-Sat. 14 hrs. $275. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

June 28—**AIDS Update: Essential Issues in Primary Care Management.** Alta Bates-Herrick Hospital at Alta Bates Auditorium, Berkeley. Wed. 7 hrs. $75. Contact: Mary Grim, (415) 540-1420.

June 30-July 1—**Euthanasia: An Old/New Dilemma for Physicians.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

July 9-12—**3rd Annual Family Practice Board Review.** UCSD at Hanalei Hotel, San Diego. Sun-Wed. 20 hrs. $355. Contact: Janice R. Turner, PO Box 2528, La Jolla 92038. (619) 459-9597.

July 10-13—**Family Practice Board Review Course.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Thurs. 25 hrs. Contact: Division of Family and Community Medicine, 400 Parnassus Ave, A-C9, San Francisco 94143-0900. (415) 476-1482.

July 10-14—**Marine Medicine 1989.** UCSD at Catamaran Hotel, San Diego. Mon-Fri. 23 hrs. $350. Contact: UCSD.

July 14—**Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Fri. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 24-28—**Sports Medicine 1989: A Practical Approach to Caring for Today's Athlete.** UCSD at The Princess Hotel, San Diego. Mon-Fri. 22 hrs. $335. Contact: UCSD.

(Continued on Page 734)

TAGAMET® (brand of cimetidine)

See complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product.*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) Injection by intravenous bolus.*

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses, for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

How Supplied: Tablets: *200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).*

Liquid: *300 mg./5 mL., in 8 fl. oz. (237 mL.) amber glass bottles and in single-dose units (300 mg./5 mL.), in packages of 10 (intended for institutional use only).*

Injection:

Vials: *300 mg./2 mL. in single-dose vials, in packages of 10 and 30, and in 8 mL. multiple-dose vials, in packages of 10 and 25.*

Prefilled Syringes: *300 mg./2 mL. in single-dose prefilled disposable syringes.*

Single-Dose Premixed Plastic Containers: *300 mg. in 50 mL. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

ADD-Vantage®* Vials: *300 mg./2 mL. in single-dose ADD-Vantage® Vials, in packages of 25.*

'Tagamet' HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Baxter Healthcare Corporation, Deerfield, IL 60015.

**ADD-Vantage® is a trademark of Abbott Laboratories.*

8RS-TG:L78B *Date of issuance Aug. 1988*

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Before prescribing, please see brief summary of prescribing information on adjacent page.

Journal of the Arizona Medical Association

ARIZONA MEDICINE

June 1989, VOL. XLVI, No. 6

Patients May Be Our Best Collaborators

Marshall B. Block, M.D.

A recent article appeared in the *Wall Street Journal* (February 27, 1989), by a visiting scholar at M.I.T. He was writing a book on collaboration between consumers and large corporations. He made the point, which appeared to him to be unique, that "clever companies should take an aggressive collaborative approach to the design of new products and services. Customers help mold the final product since the traditional perception of a customer as someone you study and then sell to is dangerously out of date. Designing with the user can be a profitable symbiotic relationship."

As I read this article, it became obvious to me that they were actually discussing the patient/physician relationship although they did not recognize it. Their revolutionary perception that "customers" need to be involved in decision making processes, whether it be in designing new computer software, hardware or other gadgetry, is hardly insightful to physicians who have been attempting to accomplish the same thing for eons.

The most successful patient/physician relationship is one in which there is a give and take, where the patient is informed regarding choices, side effects, outcome, and most importantly our lack of knowledge about many things which we accept as dogma. It seems to me that most of the problems in the patient/physician relationship have to do with miscommunication and unrealistic expectations.

My wife of twenty-three years continues to become miffed at me when I answer 95% of her questions with "I don't know." Our patients expect us to know a lot more than we really do which puts us in the uncomfortable position of thinking that we really do know a lot when in fact the "rational" decisions which we make are really very irrational. For instance, an intern called to tell me that a patient was slipping back into diabetic ketoacidosis because his serum bicarbonate level went from 23 to 20 mEq./1. This prompted aggressive maneuvers which resulted in an added day's stay in the Intensive Care Unit and multiple blood sugars, chemistry panels and blood gas determinations. When I questioned whether she based her decision on adequate data, i.e., one change in one bicarbonate determination, she emphatically said, "Of course!" I asked her how accurate she thought the serum bicarbonate determinations were and that if one did multiple determinations simultaneously what the standard error of the test itself was. She had no answer but would not budge from the position that her decision was based on solid information.

I wonder how many decisions that we all make on a daily basis are based on an inadequate foundation either because of lack of general scientific knowledge or incomplete data which could be improved by additional studies? I still recall telling a diabetic patient that she needed to have a lobectomy for pulmonary coccidioidomycosis several years ago. The patient and her family were smarter than I. They went elsewhere and got a second opinion. He suggested that conservative monitoring would do just as well and it did! We all need to consider that much of what we know is of limited value and that many times we need to transmit this to our "customers," our patients, in order for them to have better expectations of our healing powers.

I suspect that with such an approach many of the complaints to BOMEX and local grievance committees could be avoided. Better collaboration can only lead to better medical care.

Marshall B. Block, M.D., Editor

Journal of the Arizona Medical Association

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In This Issue:

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- Outcome Assessment: The Next Phase in the Health Care Revolution
- Physicians in the News
- New Members
- Health Insurance: Its Effect On Us All
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- In Memoriam
- Classified Advertising

Membership Has Its Benefits

One of the major credit cards spends an inordinate amount of advertising monies to convince you that membership has its privileges. We can't speak for anyone else, but at the Arizona Medical Association we know membership has its benefits -- and if you're not taking advantage of them, it's worth your while to take a moment to pick up the phone.

You can save a lot more than the cost of your dues if you do. ArMA's subsidiaries offer financial planning tailored for the business of medicine, investment products with a healthy rate of return, professional financial counseling, asset protection and reliable retirement plans.

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ArMA members are also eligible for extremely beneficial life/health/disability insurance plans packaged specifically for physicians. Plans have been negotiated to provide appropriate benefit amounts and protection with the highest quality service and products at the lowest rates.

In addition to these programs designed to help physicians succeed in the business of medicine, ArMA offers information which can help with the changing -- and growing -- demands imposed by the government and third party payors on the practice of medicine. Physicians with questions about licensing, government regulations, Medicare, liability insurance, risk management or third party payors, can call ArMA. If we don't know the answer, we can find out or put you in contact with someone who does.

Both the business of medicine and the demands from external forces on the practice of medicine have contributed to the stresses of medicine. ArMA is a sponsor of two programs established to help physicians cope with problems developing from stress. The Physician's Health Program offers hope for physicians with alcohol, drug or psychological problems which have impaired, or may in the future impair, professional performance. The Peer Support program offers understanding and emotional support for physicians who are being sued.

Finally, ArMA's "strength in numbers" allows its administrative staff to negotiate special programs for its members.

In the works are discount leases for automobiles and counseling regarding the sale or purchase of medical practices. A reimbursement specialist will soon be available to advise ArMA members, and MICA has said it will reduce malpractice insurance rates an average of five percent if the periodic payments bill ArMA has sponsored is signed into law by the governor.The present example of ArMA's negotiations on behalf of its members is the $11 monthly Motorola Bravo vibrating digital display pager offer from U.S. West Paging, Inc. If you're paying more than $11 monthly for your pager and you haven't yet signed up for this offer, you definitely need to call ArMA's office. This deal alone can save over half the cost of your dues!

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Dick Pearson

Financial and Estate Planning For Physicians

The art of financial planning can be described as the process of developing and implementing a total, coordinated written plan for the achievement of your financial, tax, and estate planning objectives.

A good plan should include all of the following:

Net Worth, including a complete analysis of liquid, investment, business and personal assets and liabilities. Analysis includes important ratios.

Income and Expenditures, lists income sources, basic and discretionary expenditures, income and employment taxes, and funding for long term objectives. Analyzes income and expenditures and the doctor's ability to undertake investments.

Investment Analysis, presents complete investment portfolio with an analysis of annualized rate of return, realized and unrealized short and long term capital gains and losses. Assigns an investment goal, automatically relegating funds to the proper planning area.

Business Valuation, provides a complete evaluation of a practice in terms of book value, earning, and goodwill. Evaluates business insurance.

Insurance Analysis, provides life and disability insurance needs. Lists health, homeowners, automobile, and umbrella policies. Indicates whether you are overinsured, underinsured, or properly covered based on individual information and projections.

Education and other Personal goals, for doctors with children, shows funding requirements based on childrens' ages and anticipated expenses. Provides investment analysis to reach other goals.

Retirement Planning, computes the required capital for retirement, considering both current and projected retirement plans.

Estate Planning, computes Federal Estate Tax for both doctor and spouse using both orders of death under different property ownership arrangements.

Long Range Planning

- Income Tax Planning, forecasts tax liability for future years and measures the impact of possible tax saving strategies.
- Cash Flow Analysis provides cash flow analysis and multi-year projections, including recommended funding to achieve goals.

Personal Data

A complete plan includes the location of important documents, family information, trusts and partnerships, and financial advisors.

Many physicians have had some degree of financial planning done for them. Too many, however, have not.

Ask yourself the following questions to determine the importance of planning in your personal situation.

--Are you getting all of the tax relief available to you?

--Will your savings and investments keep pace with inflation?

--Will your liquid reserves be adequate to meet emergencies and respond to opportunities?

--Will you comfortably be able to meet the rapidly rising cost of higher education as your children reach college age?

--What will it take to make you financially independent when you retire?

--Are estate taxes something that would affect your family . . . now and in the future?

--What type and how much insurance coverage do you need, and how do you minimize the cost while maximizing the benefit?

--How does your willingness to take risks impact on your average yield?

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For example, with joint taxable income of $29,800 to $71,900, you would be in the 32% combined federal and Arizona tax bracket and would need a taxable investment paying 10.66% to equal a tax-free return of 7.25%.

1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

Professional Selection Plus Surveillance A specialist in municipal bonds since 1898, Nuveen utilizes its experience, municipal research resources, and market intelligence system to select the most creditworthy bonds rated by Standard & Poor's or Moody's in categories A to AAA. Then Nuveen conducts credit surveillance over every trust portfolio until the last bond is paid.

Diversification Nuveen diversifies the bonds in each portfolio by type, purpose, revenue source behind the issue, and geographic locale. This tends to reduce your investment exposure.

No Management or Redemption Fees

Liquidity You can retain your trust units until all the bonds are redeemed. Or, you can cash in some or all of your units any business day at that day's net asset value. Inasmuch as all securities investments are subject to market price fluctuation, you could receive more or less than your initial investment.

Payment Options How do you want your tax-free money? Monthly, quarterly, or semiannual checks? Or, your trust distributions can be automatically reinvested to earn compounded tax-exempt dividends.

Reinvestment Options You can reinvest interest and principal or principal distributions only. Then, select either a tax-free money market fund or municipal bond fund. There's no charge to reinvest, and you receive quarterly reinvestment statements.

Convenience All the work of owning municipal bonds is done for you: safekeeping of securities; watching for called bonds; collecting a semiannual interest from issuers. And, receive a year-end accounting, too.

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Outcome Assessment: The Next Phase In The Health Care Revolution

It is obvious that the health care system has undergone dramatic changes in the last 25 years. It is fair to call these changes a revolution. Recently those paying the bill for health care have demanded some measure of the quality of care delivered, to see whether they are getting their money's worth. Outside of some nebulous feeling about quality, we only have outcomes as a measure of the quality of care. This then is the next phase of the health care revolution: outcome assessment. The stakes are high. The total cost of health care in 1987 was $500.3 billion dollars, a whopping 11.1% of the gross national product. Much of the blame for increasing costs is due to the lack of definition of correct practice. Put another way, "what is high quality medicine?" The assessment of quality can only be accomplished by studying the outcomes after various interventions.

Treating the health care sector as another part of the economy is upsetting though necessary. One of the hardest facts for many physicians to accept is that health care is a high technology service industry. Though a noble calling, and one dealing with life and death matters, our work and its delivery has many similarities to the hotel industry. We would do well to learn, at least a little, from the other service industries. Those organizations that measure their performance dramatically increase their chances for success. But defining quality is an illusive goal.

There are wide variations in delivery of various health services which quite understandably make health are payers skeptical of the whole system. For example, a Bostonian is twice as likely to have a carotid endarterectomy as a New Havenite, while on the other hand, the chances of having coronary artery bypass is twice as likely in New Haven as it is in Boston.[1] The problem seems to lie in the lack of consensus of physicians themselves on the correct way to practice medicine.

Some objections may initially be raised about the feasibility of the task of assessing quality by outcome in an area as complicated as medicine. There are, however, only 23 operations accounting for 60% of surgical admissions to U.S. hospitals and only 40 acute and chronic conditions make up 70% of all medical admissions. These are fairly well defined categories that lend themselves to measurement. The advent of powerful, flexible computerized systems to compile and coordinate information has also made the task far less daunting.

It is important to remember that the presence of outliers on performance measures (indicators) is not always evidence of substandard care. One complaint that physicians have about their current relationship with those overseeing the health care system is that too frequently physicians are treated as if they were delinquent school children in need of direction. A cooperative theory of Continuous Improvement has been proposed as an alternative to the current flawed theory of Bad Apples.[2]

Measurement of indicators will be an outcome assessment tool to provide information that heretofore has been only a matter of impression. The ongoing regional and national clinical trials generated by this system will be valuable in the ongoing quest for excellence in medical care. Outcome assessment is indeed the herald of the next phase in the health care revolution. Having a basic understanding of this area will do much to allay physician apprehension. We hope to communicate it's importance to physicians-in-training at the University of Arizona College of Medicine. Though it is already upon us, physicians fortunately are having a role in the development and use of these systems.

Steven Calvin, M.D.
Assistant Professor
Department of Obstetrics & Gynecology

References

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2. Berwick, DM. NEJM 1989; Vol. 320, No. 1:53-56

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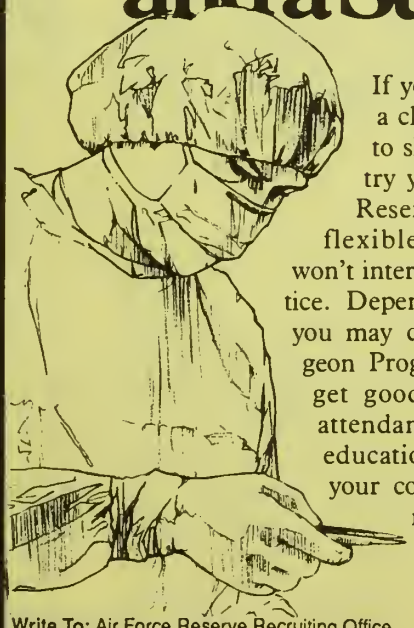

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Physicians in the News

Eugene R. Almer, M.D., P.C., of Scottsdale and Janice B. Dorn, M.D., Ph.D., of Phoenix have passed the certification exam of the American Medical Society on Alcoholism and Other Drug Dependencies (AMSAODD) and are identified by that Society as knowledgeable and expert in chemical dependence. They are the only two psychiatrists credentialed in Arizona by AMSAODD.

Five hundred forty-eight physicians throughout the country were certified this year by AMSAODD, the major national and international organization for physicians who specialize in addiction medicine. Including those certified in 1986 and 1987, there are now 1823 AMSAODD-certified physicians.

Doctors Almer and Dorn will be presented a certificate during the Society's 35th Annual Medical Scientific Conference in Atlanta on April 29. The 1989 directory of AMSAODD members (currently 3500) will identify those who are certified.

This is the third year that the innovative examination has been offered to AMSAODD members on a national basis in an effort to identify physicians who have expertise in this rapidly expanding field. The next examination is scheduled for December, 1990.

Janice B. Dorn, M.D., Ph.D.

"The field of alcohol and drug dependence treatment is growing rapidly in response to increased awareness of addiction as a major health problem in this country, said Margaret Bean-Bayog, M.D., President of the Society. "Certification is a way to identify those physicians who, by testing, have shown a mastery of the body of knowledge that has been amassed in this field."

Doctors Almer and Dorn passed a six-hour examination covering alcohol, narcotics, stimulants, cocaine, marijuana, hallucinogens, inhalants, PCP, hypnotics and nicotine, with questions equally divided between patient management and basic sciences. Basic sciences included neurophysiology, psychopharmacology, biochemistry, nutrition, and toxicology. Recertification will be required after ten years in order for the certification to remain current.

Jack A. Friedland, M.D.

Phoenix physician Jack A. Friedland, M.D., was chosen as president-elect of The American Society for Aesthetic Plastic Surgery, Inc. on April 12 at the Society's 22nd annual meeting at the Hyatt Regency Grand Cypress Hotel. Eight hundred of the nation's top plastic surgeons attended the meeting April 9-13.

Dr. Friedland, certified by the American Board of Plastic Surgery in 1975, is Chief of Plastic Surgery at Children's Rehabilitation Ser-

Continued on Page 13

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Jerry M. Calkins, M.D.
Anesthesiology
P.O. Box 5099, Dept. of
Anesthesiology, Phoenix
University of Arizona
College of Medicine - 1976

Charles R. Clinch, D.O.
Obstetrics & Gynecology
1108 W. Indian School Road
Phoenix
Texas College of
Osteopathic Medicine - 1977

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Suite 614, Phoenix
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Pritzker School of Medicine of
the University of Chicago - 1975

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of Medicine, Memphis - 1978
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Pediatrics
AZ Health Sciences Center
Pediatrics 3431, Tucson
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Internal Medicine
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State University of New York
College of Medicine,
Brooklyn - 1967

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College of Medicine - 1961

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University of Minnesota
Medical School - 1941

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University of Medicine &
Dentistry of New Jersey - 1986

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Rheumatology
AZ Health Sciences Center
Department of Internal Medicine
Tucson
Baylor College of Medicine - 1984

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2430 N. Dodge Boulevard
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Lloyd Robinson

Health Insurance: Its Effect On Us All

This text will deal with the direction that health insurance is headed, some thoughts to stimulate ideas, and how Section 89 deals with health insurance.

Due to a variety of stimuli, several adverse reactions are taking place in this arena:

- The obvious and leader, is substantil rate increases -- 20 to 35% is not unusual, and becoming common.
- Companies are removing certain health products from their portfolio.
- Companies, and especially M.E.T.'s (Multiple Employer Trusts) are going out of business.
- Underwriting requirements are becoming much more strict.

The reasons why these distasteful as well as distressing things are occurring are not material. Dealing with the situation and adjusting our thinking so we may position ourselves in a manner which will influence the future of health insurance is material!

Seek the services of a non-partial organization to research your present position.

Make every attempt to stay away from M.E.T.s. It has been known that certain large well known and respected insurance companies have established this type of trust through a third-party administrator. They stayed with it while reaping the profits of "new business" and when the claims began eating into the profits, they either increased rates (sometimes more than 100%), or bankrupted the trust.

Direct your advisor to find a company with a documented track record with regard to rate increases, claims payments, and personal service.

You'd be well advised to align yourself with a good stable company with reasonable rates. Watch out for unreasonably low rates, no matter how enticing.

Be prepared for a future "shock renewal." A common thought is, "I'll take advantage of the low rates now and jump to another carrier when they go up. The ill effects of this philosophy are multiple. Companies are becoming less willing to accept "hop-scotching" clients.

The potential is becoming uninsurable and finding oneself in a position of no choice but to stay with a company whose rates have sky-rocketed, or worse, if the company leaves the health insurance arena altogether!

The bottom line inevitably bears out that the best way is to stay with a good, long-term, stable company

When a plan is implemented, use it wisely. One cause of out of control rates is over utilization. Give your employees a reason to stay healthy. Institute rewards for getting fit and losing those extra pounds. The rewards to you are numerous. Elevation of employee morale and maintaining good rates creates a good feeling.

I'm seeing a trend beginning with some of our physician practices. They're implementing individual health policies for their employees and themselves. Some of the rationale behind this is there is less volatility in this segment of health insurance (ratewise). We can construct a more customized plan for the small practice (ie. use of different deductibles -- low for employees and higher for physicians.)

The policies are portable. They continue even after the practice is retired and are convertible to Medicare supplements at age 65. This is a growing trend that has some significant merit. Again, this may or may not fit your particular needs.

None of us in the medical community has the desire to see "free" medical services for all -- public medicine -- socialized/federalized medicine. Call it what you will, we don't want it!

Just not wanting something to happen is not good enough. We must take action and get involved.

Two groups that are pushing us ever closer to government-controlled medicine are people with AIDS and the indigent. Perhaps we should direct some of our thoughts to donating a portion of our time toward free service to these two groups and lobby the hospitals to do likewise.

Finally, on a less emotional but none-the-less equally frustrating topic -- consider the dear old Internal Revenue Service's Section 89, and how it relates to health insurance. I'll speak in depth on this topic in a subsequent article, but for now the main compliance pitfalls are:

Employees must be covered if they:

- work a minimum of 17.5 hours per week.
- work more than 6 months per calendar year.
- are 21 years of age or older.

The plan:

- must be in writing
- must be legally enforceable.
- must be created for the benefit of employees.
- must be established with an intention of maintaining them indefinitely.

Reasonable notification of benefits must be given to employees.

I welcome your thoughts. Send them to me at ArMA Headquarters. Please feel free to call me directly, 246-8901, or 1-800-482-3480 statewide toll-free so that I may assist you.

Lloyd Robinson
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Dr. Friedland

Continued from page 8

vices, Phoenix Plastic Surgery Fellowship Program.

A native of East Chicago, Indiana, Dr. Friedland received his undergraduate degree from Northwestern University in 1962 and his medical degree in 1965 from Northwestern Medical School. He completed his surgical internship and surgical residency at New York University-Bellevue Medical Center in New York City and his plastic surgery residency at the Institute of Reconstructive Plastic Surgery, New York University Medical Center.

Dr. Friedland is past president of The Staff of Crippled Children's Services, and the University Club of Phoenix.

Talk to Us!

Have you received special recognition or an award recently from your specialty society or a community organization? Do you know of a colleague who has similarly been honored for medical or community contributions?

If so, please let us know. Call Arizona Medicine at 246-8901, or 1-800-482-3480 toll-free statewide. We'd love to share the good news with medical professionals throughout Arizona.

Plague Activity Present In Arizona

The Arizona Department of Health Services (ADHS) has released recent surveillance results that demonstrate Plague activity in a number of Arizona locations. The presence of Plague antibodies in blood samples taken from coyotes and other carnivores serve as an indicator of current Plague activity. Testing for the presence of the Plague bacteria in fleas collected from trapped rodents or animal burrows is another method of surveillance.

Plague is a bacterial disease of rodents and rabbits, and sometimes of the predators that feed on these animals. It is transmitted to humans by the bite of infected fleas, or by contact with the tissues of infected rodents and rabbits when they are skinned or handled. The disease is curable if diagnosed and treated early. Health care providers should consider Plague as a possible diagnosis if a patient shows the following symptoms -- the sudden onset of fever (usually reaching 103-104 degrees), headache, weakness, nausea (sometimes), pain and/or swelling in the groin or armpits. These symptoms should be especially suspect if the patient has been exposed to rodents, rabbits and/or fleas in locations where Plague is active. Plague can also cause pneumonia. This condition is both highly contagious and usually fatal.

Plague activity, which can occur in areas above 4,500 feet elevation, has been confirmed in several locations. In Yavapai County, 9 of 11 coyotes sampled were positive for Plague southeast of Dewey, and 8 of 15 coyotes were positive for Plague southwest of Kirkland. Plague-positive bloods were also taken from coyotes west of Prescott Valley and approximately 30 miles north of Prescott. In Coconino County, 1 of 4 coyotes were Plague-positive east of Mormon Lake. In Greenlee County, 2 of 3 coyotes were Plague-positive approximately 25 miles northwest of Morenci. Finally, in Cochise County 2 of 9 coyotes were Plague-positive approximately 18 miles southeast of Sunizona near the Chiricahua Mountains.

People visiting or living in Plague-active areas should take certain precautions to avoid exposure to the disease:

» Do not handle sick or dead animals.

» Avoid exposure to rodent burrows and fleas.

» Prevent pets from roaming. Wandering animals can become infested with Plague-infected fleas and transmit them to humans.

» Dust pets with flea powder at least weekly.

» Wear rubber gloves when skinning rabbits and preparing them for cooking.

In the event of illness with symptoms compatible with Plague, consult a physician immediately.

In Memoriam

"Lives of great men all remind us
We can make our lives sublime,
And, departing, leave behind us
Footprints on the sands of time."

A Psalm of Life, by Henry Wadsworth Longfellow (1807-1882)

Louis Kossuth, M.D., M.P.H., 1913-1989

The footprints left by Louis Kossuth (1913-1989) not only are deeply and firmly impressed upon the sands of time -- they have left their indelible marks upon the sands of Arizona, the records of the nation's military establishment and in the annals of the world's medical progress.

His list of accomplishments in the health field, locally, nationally and internationally, is a long and distinguished one.

An indirect descendant and namesake of the Hungarian revolutionary statesman and lawyer who, in 1849, won brief but significant independence for his native land from Austria, Dr. Kossuth earned his M.D. degree in 1939 at Western Reserve University (now Case Western Reserve University) in Cleveland, Ohio. Seven years later, in 1946, he earned his M.P.H. degree from Harvard University's School of Public Health in Boston.

Shortly after his graduation from Reserve in 1939, Louis Kossuth and Velma Sorenson were married. She had received her Master's degree in nursing from Reserve's Frances Payne Bolton School of Nursing also in 1939.

Born August 13, 1913, in Wheeling, West Virginia, Dr. Kossuth's entire medical career was spent in public service. He never entered the private practice of medicine.

After completing his internship in 1941, despite some reluctance by the military to allow him to do so, Dr. Kossuth entered the U.S. Air Force, retiring in 1969 with the rank of colonel.

During his military service, marked by many notable achievements, Dr. Kossuth rose to become chief of preventive medicine at the Pentagon, deputy commander of the U.S. Air Force School of Aviation Medicine, commander of the USAF Medical Service School, and surgeon general of the USAF Air Defense Command and of NORAD (North American Air Defense Command).

He served with distinction throughout World War II and in Korea and was an important figure in the affairs of the World Health Organization and other international and national health groups.

Despite his many outstanding achievements, the honors of which Louis Kossuth was most proud were his successive terms (1956-1961) as Fellow, Regent and President of the American College of Preventive Medicine.

In Arizona, Dr. Kossuth was the State's last health commissioner (1969-1974). Despite legislative opposition that faced him at almost every turn, he won significant victories in his battle to improve Arizona's public health status, particularly in the areas of air and water pollution.

Louis Kossuth was a giant in his field. His untimely passing leaves a void that not easily nor quickly can be filled and he will be missed more than can be comprehended now. Arizona is fortunate in having had him as one of its most distinguished and capable citizens.

In addition to his wife, Dr. Kossuth is survived by four children: Dr. Karen Kossuth, Professor of Linguistics at Pomona College in California; George J. Kossuth, a computer software engineer in Boston; Dr. Sue Kossuth, chief plant physiologist with the U.S. Department of Agriculture in Gainesville, Florida, and Sally L. Kossuth, who will be awarded her degree in medicine this summer.

Farewell, my friend! Ended is the flight,
And He whose hands upheld you in the air,
Whose spirit guided you in darkness and in light,
Has called you home. I bow my head in prayer.

Adapted from a poem by Gunter Von Huenefeld (1893-1929).

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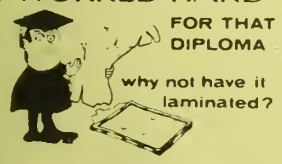

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Clinical Investigation

Phenytoin Absorption in Volunteers Receiving Selected Enteral Feedings

JAMES R. GUIDRY, PharmD; THOMAS F. EASTWOOD, MD; *and* STEVEN C. CURRY, MD, *Phoenix*

Phenytoin absorption is reportedly significantly altered in the presence of continuously administered enteral feedings, resulting in subtherapeutic serum phenytoin concentrations and loss of seizure control. We administered 500 mg of phenytoin as the suspension to five volunteers who were not receiving enteral feeding, again while they ingested protein hydrolysate enteral feedings hourly, and again during hourly ingestions of meat-base enteral feeding. Serum phenytoin concentrations, measured 3, 6, 9, 12, and 24 hours after phenytoin ingestion, were lowest with protein hydrolysate feedings. Mean serum phenytoin concentrations were consistently higher with the meat-base feeding than with the protein hydrolysate formula, although levels did not reach those of the control period. These data are in keeping with our previous observation that it is easier to attain therapeutic serum phenytoin concentrations in patients receiving a meat-base enteral feeding than in those receiving a protein hydrolysate formula.

(Guidry JR, Eastwood TF, Curry SC: Phenytoin absorption in volunteers receiving selected enteral feedings. West J Med 1989 Jun; 150:659-661)

The first documentation of poor absorption of oral phenytoin in patients receiving continuous enteral tube feedings was by Bauer in 1982.[1] Since then others have confirmed the ability of enteral feedings to prevent the absorption of phenytoin.[2,3] Several hypotheses have been suggested in attempts to explain the problem, including the high pH of phenytoin oral suspension, the binding of phenytoin to sodium and calcium caseinates in the enteral feedings, and certain other food constituents binding to phenytoin and decreasing its absorption (aluminum, copper).[4,5]

Efforts to overcome impaired phenytoin absorption, such as altering or interrupting feeding schedules, have been largely unsuccessful.[6] Holtz and colleagues studied the in vitro compatibility of phenytoin mixed with various enteral feedings.[7] They found wide variations in phenytoin concentrations in enteral feedings after the addition of phenytoin suspension (phenytoin acid), which corrected when the injectable form of the drug (phenytoin sodium) was used. We are not aware of any clinical studies resulting from Holtz's report.

We and others found that phenytoin doses of 1,800 mg per day and greater were required to reach therapeutic serum concentrations when protein hydrolysate enteral feedings were used.[1,8] Our own case report suggested that using an enteral feeding formula with a meat base rather than a protein hydrolysate improved phenytoin absorption considerably.[8] The dose of phenytoin required to maintain therapeutic serum concentrations could be reduced to 400 mg per day when the meat-base formula was substituted.

A possible risk of using high phenytoin doses to overcome poor absorption in the presence of protein hydrolysate feedings is that phenytoin intoxication may result if enteral feedings are discontinued.[8]

To confirm our clinical observations, we modified the original study of Bauer,[1] comparing phenytoin absorption in volunteers receiving either a meat-base or protein hydrolysate enteral feeding. We think this is the first report comparing phenytoin absorption in volunteers receiving different enteral feedings.

Subjects and Methods

Five experimental subjects who attained peak serum phenytoin concentrations of at least 5 mg per liter after a single ingestion of 500 mg phenytoin as the suspension were selected for the experimental group. This was done to lessen the possibility that serum phenytoin concentrations would fall below the limit of sensitivity of the assay during the study period. The testing of seven subjects was required to select these five volunteers.

These five male volunteers were nonsmokers, had no medical illnesses, and had taken no medication during the previous three months. Their mean age was 32.8 years (range 27 to 43), and their mean body weight was 71.8 kg (range 57 to 77).

We administered 500 mg of phenytoin as the suspension to these five volunteers without administering enteral feeding, again while they ingested protein hydrolysate enteral feeding hourly, and again while they ingested meat-base enteral feeding hourly.

Phenytoin Suspension, 125 mg per 5 ml (Parke Davis, lot numbers 950d5L, 11976L, and 11306L), was used in this study. Serum phenytoin levels were measured by fluorescent

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This study was supported in part by a grant from Sandoz Nutrition.

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TABLE 1.—*Ingredients of Osmolite (Protein Hydrolysate) and Compleat Modified (Meat-Base) Enteral Food Formulas*

Product	*Osmolite (Ross)*	*Compleat Modified (Sandoz)*
Calories/ml	1.06	1.07
Protein source	Sodium and calcium caseinate, soy protein isolate	Beef, calcium caseinate
Carbohydrate source	Hydrolyzed cornstarch	Hydrolyzed cereal, fruit, vegetables
Carbohydrate concentration, grams/liter	145	141
Fat source	Medium chain triglycerides, corn oil, soy oil	Beef, corn oil
Fat concentration, grams/liter	38.5	37.0
Dietary fiber, grams/8 oz	0.0	3.4

polarization immunoassay (Abbott Laboratories). In our laboratory this method has a sensitivity of 1.2 mg per liter with coefficients of variation of 5% at 5.2 mg per liter and 1.2% at 26.2 mg per liter.

Control Period

After eight hours of fasting, 500 mg phenytoin as the suspension (20 ml) was ingested at 8 AM. Subjects were then allowed food and drink ad lib. Blood specimens were drawn for measuring the serum phenytoin concentration 3, 6, 9, 12, and 24 hours after phenytoin ingestion.

Protein Hydrolysate Ingestion

Following a 14-day washout period, the subjects began drinking 100 ml of protein hydrolysate enteral feeding (Osmolite, Ross Laboratories) every hour 14 hours before receiving a 500-mg phenytoin suspension (20 ml) at 8 AM. They continued to drink 100 ml of the formula every hour for 12 more hours (26 hours total). Blood specimens were drawn for measuring serum phenytoin concentrations 3, 6, 9, 12, and 24 hours after the ingestion of phenytoin.

Meat-Base Ingestion

Following another 14-day washout period, the protocol for the protein hydrolysate period was repeated, except that a meat-base enteral feeding (Compleat Modified, Sandoz Nutrition) was used instead.

Statistical Methods

A two-way analysis of variance (ANOVA) with time and group (type of enteral feeding) as main effects was done on serum phenytoin concentrations, with $P < .05$ arbitrarily selected as representing statistical significance. A one-way ANOVA with the group as the main effect also was done at each time interval.

Results

Using the two-way ANOVA, the group was significantly different as a main effect ($P < .01$). Time as a main effect was not significant ($P = .35$).

Data are summarized in Figure 1, with P values at each time interval representing results of the one-way ANOVA.

Discussion

Like Bauer,[1] we found the protein hydrolysate formula to significantly lower serum phenytoin concentrations as compared to the control period. When receiving the meat-base formula, volunteers consistently had mean serum phenytoin concentrations higher than when drinking the protein hydrolysate preparation, although levels did not reach those of the control period. The greatest difference between the two enteral feeding groups appeared to be at three and six hours after phenytoin ingestion.

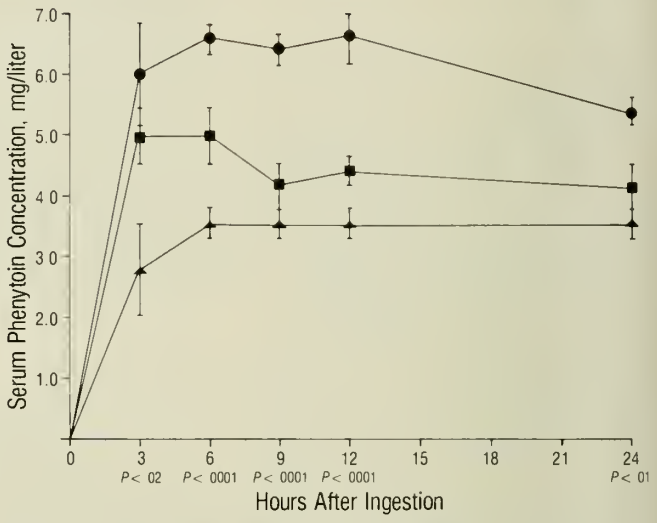

Figure 1.—The graph shows serum phenytoin concentrations versus time after ingestion. Phenytoin concentrations are expressed as mean ± standard error. ● = control group, ■ = meat-base group, ▲ = protein hydrolysate group

Although the area under a time-concentration curve is generally used as a measurement of drug absorption, the saturable elimination kinetics of phenytoin caused us to compare serum phenytoin concentrations only at various time intervals, as others have done.[1]

While it might be argued that delayed, rather than incomplete, phenytoin absorption may account for lower serum phenytoin concentrations in those receiving enteral feedings, we do not think this to be the case. Delayed, but complete, absorption should eventually allow for an attainment of therapeutic drug concentrations with repeated dosing. However, investigators have consistently noted difficulty in attaining therapeutic phenytoin concentrations when large doses of oral phenytoin have been repeatedly administered to those receiving protein hydrolysate feedings, implying an impaired absorption of phenytoin.[1,7,8]

The differences in phenytoin absorption noted previously[8] and in this study presumably are due to differences in the contents of the two formulas. The meat-base formula has different protein, carbohydrate, and fat sources from the protein hydrolysate feeding (Table 1). The percentages of calories from protein, carbohydrate, and fat in the two formulas are similar. An obvious difference between the formulas is in the dietary fiber content. The meat-base formula has 3.4 grams of fiber per 8 oz, while the protein hydrolysate formula has none. If dietary fiber is influencing the absorption of phenytoin, it may do so by complexing with and inactivating

a substance in feedings that binds phenytoin, or it may alter gastrointestinal transit time.

Summary

We have confirmed that a protein hydrolysate enteral feeding interferes with the absorption of phenytoin as the suspension. We present data indicating that phenytoin is more easily absorbed in volunteers receiving a meat-base enteral feeding than in those receiving a protein hydrolysate formula. These data are in keeping with our experience in that it is easier to achieve therapeutic serum phenytoin concentrations in patients receiving continuous enteral feedings with a meat-base formula than in those receiving a protein hydrolysate product.

A major difference between the two formulas is in the quantity of dietary fiber. We are presently examining other enteral feedings containing fiber to determine if they also allow therapeutic serum phenytoin concentrations to be easily attained.

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Correct Running Pace

WHEN YOU'RE RUNNING, run at a pace allowing you to *talk* with someone. If you can't converse, you're going too fast. You must have fun. I see runners going past, and I feel like going over and stopping them. They're not supposed to look like that. When I run, I put my body on automatic pilot. Because I want to think, I run at a thinking pace. And you have the ability then to dissociate, just as Oliver Wendell Holmes talked about walking. He said, "Walking becomes so automatic, it frees the mind." That's what the runner's high is. Running becomes so automatic, it frees the mind. People say, "Is there a runner's high?" Of course, because there was a walker's high. Read Stevenson, Hazlitt, Thoreau, Wordsworth, Kierkegaard, Kant. You find out about runner's high, because all of those geniuses who wrote the classics that we read, wrote those books while they were walking. And you don't do that if it hurts. You do that because it's comfortable.

—GEORGE SHEEHAN, MD

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Clinical Medicine

Surgical Management of Traumatic Disruption of the Descending Aorta

J. NILAS YOUNG, MD; ROBERT J. STALLONE, MD; LEIGH I. G. IVERSON, MD; COYNESS L. ENNIX, Jr, MD; ROGER R. ECKER, MD; *and* IVAN A. MAY, MD, *Oakland, California*

During an 11½-year period, 20 consecutive patients presenting with a traumatic disruption of the proximal descending aorta underwent an emergency operative repair. The mean age was 26 years (range 15 to 62), and 13 (65%) were male. Associated injuries were frequent and required additional major operative procedures in half of the cases. Two patients died as a result of associated intracranial injuries, for a hospital survival of 90%. The operative repair was accomplished by graft replacement of the involved segment of the aorta in all but one patient who underwent a primary repair. Simple aortic crossclamping was used in 8 patients (40%) and heparinless femoral-femoral venoarterial bypass in 12 patients (60%). Neither renal failure nor paraplegia developed in any of the patients. Four patients required thoracic reoperations. These results indicate that an aggressive multidisciplinary surgical approach can produce favorable results in patients with traumatic descending aortic injuries.

(Young JN, Stallone RJ, Iverson LIG, et al: Surgical management of traumatic disruption of the descending aorta. West J Med 1989 Jun; 150:662-664)

Traumatic disruption of the descending thoracic aorta due to blunt chest trauma continues to be a challenging surgical problem. It has been our policy to surgically repair these lesions as soon as the diagnosis has been established and associated injuries assessed and addressed. In this report, we review the results of this approach.

Patients and Methods

Between January 1975 and July 1986, emergency surgical repair was carried out on 20 consecutive patients presenting with a traumatic disruption of the proximal descending aorta. All patients were referred from other institutions following an initial evaluation. The mean age was 26 years (range, 15 to 62), and 13 were male. The time from injury to aortic operation averaged 18 hours (range, 2 to 96). Of the 20 patients, 17 (85%) had associated injuries, and 11 (55%) had multiple associated injuries. Ten of the patients required additional major operative procedures for these associated injuries (Table 1). The most commonly required additional major operation was splenectomy (3 patients; 15%), followed by orthopedic and neurosurgical interventions.

Operative repairs were accomplished by replacing the involved segment of the aorta with an interpositional Dacron graft. Limited resection of the disrupted aorta was done to preserve all intercostal vessels in the distal segment. We used 3-0 polypropylene sutures placed in a running fashion. The proximal aortic crossclamp was placed between the left subclavian and left carotid arteries, and the distal aortic clamp was placed as close as possible to the tear while allowing an adequate tissue cuff for the distal anastomosis. One patient underwent a primary aortic repair. This was accomplished by simple reapproximation of the limited area of aortic disruption.

Two different approaches were used for distal aortic perfusion. Heparinless femoral-femoral venoarterial bypass (HFVAB) was used in 12 patients (60%). The specific elements of this technique have been previously described.[1-4] Briefly, a long (26F) polyvinyl-polymethane bonded catheter is inserted through the femoral vein into the right atrium to collect mixed venous blood, which is then returned to the left femoral artery by way of a roller pump, thus perfusing the abdominal viscera and distal thoracic aorta (Figure 1). Perfusion rates range from 1,500 to 2,000 ml per minute and may be adjusted to control the cardiac preload. An inspired oxygen concentration of 100% during the aortic crossclamping helps increase the oxygen content of the perfused mixed venous blood. The average crossclamp time in this group of patients was 46 minutes (range, 34 to 98).

Simple aortic crossclamping was used in eight patients (40%). Proximal hypertension in this group and in the group with HFVAB could be managed by the intravenous administration of sodium nitroprusside or trimethaphan camsylate. A mean proximal arterial pressure is maintained in the range of 60 to 90 mm of mercury. The average crossclamp time in this group was 23 minutes (range, 12 to 32). The decision to use simple crossclamping versus HFVAB was made by the operating surgeon.

Results

All but 2 of the 20 patients (90%) survived. The two hospital deaths occurred within 72 hours of the aortic repair and were due to associated massive intracranial injuries. Both patients had obvious critical neurologic injury and un-

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derwent a craniotomy before the aortic repair. They were declared brain dead following the aortic operation, and life support was electively terminated. Neither renal failure nor paraplegia developed in any of the survivors. Paraparesis developed in one patient in the HFVAB group five days postoperatively, which ultimately cleared.

Four patients required a thoracic reoperation, one for early surgical bleeding, one for chylothorax, one for an expanding pseudoaneurysm at the distal anastomotic suture line, and one had an aortic obstruction at the proximal anastomotic site.

The chylothorax was managed by ligating the thoracic duct at the supradiaphragmatic level through a right thoracotomy. The pseudoaneurysm was repaired by direct suture. The obstructive lesion appeared to have resulted from a compressive hematoma at the level of the proximal anastomosis (distal aortic arch). The clinical findings in this patient were those of upper body hypertension and diminished femoral pulses. A second postoperative aortogram revealed the presence of obstruction at the proximal anastomotic site. At the second operation, a tubular Dacron graft was placed between the ascending aorta and the proximal descending thoracic aorta, thus bypassing the obstruction. The patient had no postoperative difficulty and is now normotensive with equal upper and lower extremity pulses.

Comments

Our results indicate that an aggressive surgical approach can be associated with favorable results in patients with dissecting aortic injuries. Earlier series reported renal failure

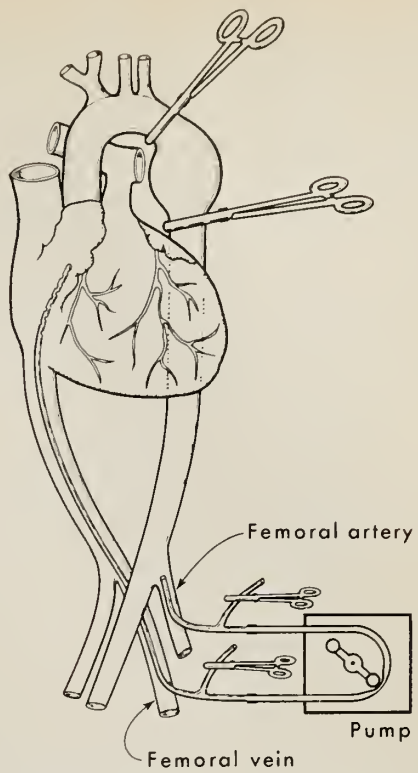

Figure 1.—Venous blood is drained from the right atrium by way of a long 26F cannula and is returned to the femoral artery by a roller pump. The lower part of the body is perfused with mixed venous blood.

TABLE 1.—*Profile of 20 Patients Having Emergency Operative Repair of Proximal Descending Aorta*

Patient	Age, yrs	Sex	Length of Time Injury to OR, h	Associated Major Injuries	Surgical Procedures for Associated Injuries	Significant Complications
1	21	♂	24	Fractured femur	None	Chylothorax; reoperation twice
2	23	♀	8	Massive cerebral contusion	Craniotomy	Died
3	42	♂	48	Multiple rib fractures	Popliteal embolectomy, fasciotomy, below-knee amputation	Pulmonary embolus; popliteal embolus
4	16	♂	12	Cerebral concussion	None	Pneumonia
5	18	♂	12	Ruptured spleen	Splenectomy	None
6	62	♀	12	Flail chest, fractured ankle	Open reduction right ankle	None
7	40	♂	1	Flail chest	None	None
8	26	♂	2	None	None	None
9	17	♂	24	Fractured jaw	None	None
10	25	♀	8	Ruptured spleen, fractured ankle	Splenectomy, open reduction right ankle	Hypertension
11	23	♂	24	Cerebral concussion, dislocation of left hip	Open reduction left hip	None
12	18	♂	8	Left hemopneumothorax, lumbar spine fracture	None	None
13	34	♂	8	Dislocated right knee, liver lacerations	Laparotomy, open reduction right knee	Surgical bleeding requiring reoperation; respiratory insufficiency
14	21	♂	36	Multiple rib fractures, myocardial contusion, ruptured spleen	Splenectomy	Respiratory insufficiency; hypertension
15	23	♀	8	Skull fracture, multiple trauma	Splenectomy; nephrectomy	Died 5 days postoperatively due to head injury
16	15	♂	6	Cranial epidural hematoma; fractured right tibia, fibula	Craniotomy	Pneumothorax, coarctation on anastomotic site
17	18	♂	96	Ruptured bladder; fractured left maxilla, pelvis, both legs	Laparotomy; bladder repair	Pleural effusion; ICU psychosis
18	59	♀	12	Left pneumothorax, fractured pelvis	None	Hypertension
19	24	♂	24	None	None	Anastomotic leak 2 wk postoperatively; reoperation twice; paraparesis 5 days postoperatively
20	21	♀	12	Multiple fractures both legs	None	None

ICU=intensive care unit, OR=operating room

rates ranging from 10% to 29%.[5,6] In contrast, there were no episodes of renal failure or paraplegia in our patients. The one episode of paraparesis that developed several days postoperatively was presumably due to dissection or hematoma formation distal to the surgical site with resulting compromise of spinal cord blood flow.

Because many of these patients had multiple injuries, including intracranial injuries, we have preferred to use techniques that do not require heparin therapy. On the basis of these results, heparinless femoral-femoral venoarterial bypass and simple aortic crossclamping are safe alternatives. With simple aortic crossclamping, however, the crossclamp times should probably be relatively brief because no distal organ protection exists with this technique.

We have preferred the use of HFVAB over aortic shunts that must be inserted into either the aortic arch, the ascending aorta, or the left ventricular apex. When HFVAB is used, the shunt tubing is completely out of the operative field. This obviates the necessity for dissecting mediastinal structures or portions of the aorta not involved with the operative repair. This may be particularly beneficial when an extensive mediastinal hematoma is present or when the patient has active bleeding from the area of aortic disruption. Because the HFVAB shunt tubing involves a long venous catheter, the pump must be kept in a continuous mode to prevent clotting within the tubing in an unheparinized patient. We have had no complications arising from residual thrombosis on either the venous or arterial side following HFVAB.

When possible, particularly in young patients, it is preferable to do a primary repair. Unfortunately, in many cases the aorta may be almost completely transected, and the recoiling of the proximal and distal ends makes it difficult to do a primary repair. Therefore, graft insertion is necessary to avoid tension on the suture lines. The experiences of others suggest that the indications for a primary repair may be expanded.[7]

It is apparent from our series that multiple associated injuries, with the exception of massive intracranial injuries, can often be dealt with effectively. The management of multiple injuries requires setting priorities. Acute intracranial injuries or life-threatening intra-abdominal injuries should be managed initially if the aortic disruption does not appear to be actively bleeding. An avoidance of systemic hypertension during the management of the associated injuries is especially important to prevent extension or rupture of the aortic tear. If active bleeding appears to be occurring from the aortic rupture site, or there is evidence of impending progression of the lesion as shown by increasing pain or compromise of the distal circulation, then the aortic injury should be managed initially. Systemic hypertension should be avoided postoperatively to prevent bleeding or dissection of the aortic repair. An efficient coordination of the various surgical disciplines involved is of the utmost importance to ensure survival of patients with multiple major injuries.

In conclusion, the present-day results of the management of thoracic aortic injuries due to blunt trauma can be associated with a high salvage rate even in the presence of multiple associated injuries. The prompt recognition and management of both the aortic lesion and other major injuries should result in a low incidence of mortality or residual morbidity.

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The Use of Fine-Needle Aspiration Biopsy in Children

MICHAEL B. COHEN, MD, *New York;* KENT BOTTLES, MD; ARTHUR R. ABLIN, MD; *and* THEODORE R. MILLER, MD, *San Francisco*

Fine-needle aspiration biopsy has become increasingly popular for evaluating both palpable and nonpalpable masses. Judging from the current body of literature, this procedure is underused by American pediatricians. We report a series of 84 pediatric patients—younger than 16 years—who underwent 92 fine-needle aspiration biopsies to evaluate a large variety of masses. The results of 51 (55%) were benign, and 33 (36%) biopsies revealed malignancy. In two cases (2%) the findings were suggestive of malignancy, and in six cases (7%), insufficient material was rendered for diagnosis. Either histologic or clinical follow-up or both were available for 85 procedures. Based on these cases, the sensitivity was 97% and the specificity was 95%, indicating that fine-needle aspiration biopsy is a good method for screening and observing patients for various malignant tumors in a variety of organs.

(Cohen MB, Bottles K, Ablin AR, et al: The use of fine-needle aspiration biopsy in children. West J Med 1989 Jun; 150:665-667)

Although used successfully in Europe for 35 years, fine-needle aspiration biopsy (FNAB) has only recently been gaining interest in the United States.[1] The procedure uses 22- to 25-gauge needles for the biopsy of palpable and nonpalpable masses without anesthesia. Advantages attributed to FNAB include a rapidity of diagnosis, minimal morbidity and mortality, low cost, and a high degree of accuracy. In a recent survey of private practice clinicians in San Francisco who treat adult patients, 83% (307/369) anticipated that FNAB would be used more frequently in the future.[2]

Until recently, the application of FNAB to the pediatric population has largely been ignored in the American FNAB and pediatric literature. Previous reports in this country have studied its use in only small series of pediatric patients.[3,4] In this report, we present the largest United States series of pediatric FNABs; this study includes 92 FNABs from pediatric patients seen at the University of California, San Francisco (UCSF), and the San Francisco General Hospital (SFGH) medical centers.

Patients and Methods

Between 1982 and 1985, the UCSF and SFGH FNAB services did more than 7,000 procedures. All reports of FNABs from patients younger than 16 years of age were obtained from the files of the UCSF Cytology Registry and the teaching files of SFGH. In all, pathology reports, slides, and selected medical records of 84 study subjects (43 male, 41 female) were reviewed, and FNAB reports obtained from them. Five patients had two procedures, and one had four biopsies. The mean age of the patients was 5.8 years; the youngest patient was 9 months.

The FNABs were done as previously described.[5-7] All FNABs were done by an attending cytopathologist or by an invasive radiologist in cooperation with the FNAB service. Briefly, the needle, attached to a syringe mounted onto a syringe holder, was introduced through alcohol-wiped skin into the mass. One hand fixed the mass between two fingers while the other hand manipulated the needle back and forth within the mass with full suction exerted on the syringe. The procedure was terminated by releasing the suction before removing the needle from the mass. While an assistant applied pressure to the puncture site, the aspirator prepared air-dried slides for May-Grünwald-Giemsa staining and alcohol-fixed slides for Papanicolaou staining. For nonpalpable masses, computed tomographic scans or ultrasonography were used to precisely localize the biopsy site, and a fast stain was done by the attending cytopathologist to ensure the adequacy of the specimen. Some of the patients required sedation for the biopsy of nonpalpable masses.

Sensitivity and specificity were calculated according to the definitions of Galen and Gambino.[8] Several of the patients described in this study have been previously reported.[9,10]

Results

The fine-needle aspiration biopsies revealed 51 benign lesions (55%) and 33 malignant neoplasms (36%). Of the remaining eight cases, six (7%) had insufficient material for diagnosis and in two (2%), the results were suggestive of malignancy.

Table 1 lists the anatomic sites at which biopsies were done. Five sites accounted for 75% of all specimens: lymph nodes, extremities, head and neck region, abdomen, and orbit. Table 2 lists the malignant diagnoses. Of the 33 malignant cases, 31 had previous, concurrent, or subsequent surgical biopsies in the same area as the FNAB; there were no

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ABBREVIATIONS USED IN TEXT

FNAB = fine-needle aspiration biopsy
SFGH = San Francisco General Hospital [Medical Center]
UCSF = University of California, San Francisco

false-positive FNAB results in these cases. The other two cases were treated without histologic confirmation or comparison with previous histologic material. The FNAB diagnoses of these two cases were lymphoma and neuroblastoma. The malignant nature and type of neoplasm of these two FNAB diagnoses were based on the light-microscopic appearance, enzyme histochemistry, immunohistochemistry, electron microscopy, and clinical course.

Of the 51 patients with benign findings, 13 underwent a surgical biopsy in the same area as the FNAB, and no malignant lesions were found. An additional 27 cases had a follow-up of one to four years' duration, and no malignancy developed at the FNAB site. Follow-up on the remaining 11 cases was not available.

Six cases had insufficient material for diagnosis. On only one of these was a surgical biopsy done, and it showed histiocytosis X involving the skin. The other five patients have been observed clinically for one to four years and show no evidence of disease. Both patients with suggestive findings underwent a surgical biopsy, and the results were histologically benign. The sensitivity of our series, including only those patients who had histologic or clinical follow-up, was 97%. The corresponding specificity was 95%. There were no complications.

TABLE 1.—*Biopsy Site of Fine-Needle Aspiration Biopsy*

Site	*Cases, No.*
Lymph node	23
Extremities	13
Head and neck	12
Abdomen	11
Orbit	9
Salivary gland	7
Thorax	6
Back	3
Central nervous system	3
Skin	2
Pharynx	2
Thyroid	1
Total	92

TABLE 2.—*Malignant Diagnoses by Fine-Needle Aspiration Biopsy**

Diagnosis	*Cases, No.*
Rhabdomyosarcoma	9
Lymphoma/leukemia	5
Neuroblastoma	4
Retinoblastoma	3
Wilms' tumor	2
Undifferentiated small-cell tumor	2
Astrocytoma	1
Medulloblastoma	1
Adenocarcinoma	1
Ewing's sarcoma	1
Undifferentiated sarcoma	1
Histiocytosis X	1
Endodermal sinus tumor	1
Undifferentiated germ cell tumor	1

*32/33 cases were correctly identified by fine-needle aspiration biopsy; there was 1 false-negative case, a retinoblastoma.

Discussion

Despite increased interest in this country, FNAB has been used predominantly to diagnose neoplasms in adults. The adult FNAB literature has established that it is a safe diagnostic procedure. A literature review by Livraghi and coworkers of 11,700 abdominal FNABs revealed 1 death due to pancreatitis (0.008%) and 6 patients with major complications (0.05%).[11] Similar results have been obtained from about 17,000 prostatic FNABs done in Sweden, wherein there were 11 major complications and 1 death.[12] Fears of tumor seeding along the needle tract and of decreased survival rates as a result of a hematogenous spread of tumor cells have been allayed by studies that showed similar survival rates for patients with FNAB-diagnosed breast or kidney cancer and for control groups diagnosed by open surgical biopsies.[13,14]

Although scattered reports from other countries of pediatric FNAB use exist,[15-17] only in the past few years have any American pediatric series been published. In 1983 Schaller and colleagues reported on 32 infants and children who underwent FNAB of suspected malignant neoplasms.[3] Of the 32 FNABs, 19 revealed malignancy, and there were no complications or false-positive or false-negative results. In 1984 Taylor and Nunez reported 64 FNABs from 56 pediatric patients in which there were 19 malignant diagnoses, a sensitivity of 76%, and a specificity of 100%.[4]

Our present study confirms the conclusions reached by investigators in other adult and pediatric series. We found that FNAB can be useful in diagnosing suspected malignant tumors; the sensitivity and specificity rates of FNAB in our series were 97% and 95%, respectively; no complications occurred in our patients.

The cells and tissue clusters obtained by FNAB can be analyzed by a number of contemporary diagnostic methods. Enzyme and immunohistochemical tests of plastic-embedded sections from FNABs are useful in the differential diagnosis of small round-cell tumors of childhood. For example, a diffuse staining with acid phosphatase was observed in 6/6 neuroblastomas.[9] Such staining has not been seen in leukemias, lymphomas, or rhabdomyosarcomas. Other researchers are investigating the use of electron microscopy, computer-based image analysis, and measurements of DNA synthesis.[1,18-20] When fully developed, these techniques may allow us to more precisely identify tumors by FNAB and to more accurately predict a tumor's biologic behavior.

Although FNAB is predominantly used to evaluate suspected malignant lesions, it can also successfully diagnose inflammatory masses. In the present study, the FNAB specimen of a benign lesion of a child's neck mass revealed granulomas and acid-fast bacilli, thus establishing the diagnosis of mycobacterial infection. Even when a causative organism could not be seen on the FNAB smear, a culture of a portion of the aspirated specimen was often successful in identifying the cause of inflammatory masses in adults.[21] In an article on the management of lymphadenitis in children, FNAB was advocated as a diagnostic and therapeutic procedure for all children with fluctuant lymph nodes.[22]

In 1933 Stewart observed that "diagnosis by aspiration is as reliable as the combined intelligence of the clinician and

the pathologist makes it."[23] This statement is still true today, and it applies to the use of FNAB in children. Close cooperation between clinician, radiologist, and pathologist is essential if the FNAB is to be accurate. We have found that errors in any of the four steps of FNAB—biopsy, smear, interpretation, and communication of results—can adversely affect the accuracy of the procedure. Some studies have emphasized that the diagnostic accuracy of FNAB appears to be highest in centers where the biopsies, smears, and interpretation of findings are done by the same person.[1] For this reason, we have established a centralized pathology-based FNAB service staffed by experienced attending cytopathologists who do and interpret the FNABs. When interpreting pediatric FNABs, it is also imperative that the cytopathologist know the clinical history, age, sex, radiologic findings, the exact size of the lesion, and the chemotherapeutic and radiotherapeutic histories of the patient. Communication with the child's physician is essential to understand the differential diagnosis and the selection of appropriate diagnostic studies.

Implications

Fine-needle aspiration biopsy is an increasingly popular method for evaluating a variety of masses and can readily be applied to pediatric patients. It is a safe procedure with no or minimal morbidity and mortality, and fears about tumor spread have not been supported by the literature.[1,11-14] Other advantages include its relatively low cost, its accuracy, and the rapidity with which a diagnosis can be rendered. Fine-needle aspiration biopsy need not replace the open surgical biopsy, but it can be a valuable tool for screening both palpable and nonpalpable masses, to follow up patients with a history of malignancy, and as a means of doing a biopsy on patients who are at an increased risk from surgical procedures. For its diagnostic potential to be realized, however, pediatricians must understand the strengths and weaknesses of this test and its technical difficulties.

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Clinical Review

Hepatitis B in Pregnancy

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Chronic infection with the hepatitis B virus can result in the development of serious liver disease such as chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. Vertical transmission from infected mothers to infants is thought to be partially responsible for the high prevalence of infection in certain high-risk groups. Immunoprophylaxis using hepatitis B vaccine and hepatitis immune globulin has been highly effective in decreasing the probability of chronic hepatitis B virus infection in infants with exposure. Previously, the Centers for Disease Control recommended screening pregnant women considered at high risk of hepatitis B infection to detect newborns who would benefit from postnatal immunizations directed at preventing the HBV carrier state. Because of the poor sensitivity of high-risk criteria in distinguishing pregnant women who harbor the hepatitis B virus, these recommendations have recently been revised to call for the routine screening of all pregnant women in the United States.

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Our understanding of the wide spectrum of hepatitis B viral infection has broadened dramatically since the discovery of the Australian antigen by Blumberg in 1965.[1] Using modern serologic and immunohistochemical markers and sophisticated hybridization techniques, investigators have uncovered the role of the hepatitis B virus (HBV) in the development of acute and chronic hepatic infections. Convincing evidence has associated the hepatitis B virus with the development of serious long-term sequelae such as chronic active hepatitis, cirrhosis, and primary hepatocellular carcinoma.[2] Epidemiologic research has also revealed a surprisingly high prevalence in certain populations. Data suggest that unlike the hepatitis A virus, another common cause of viral hepatitis, the hepatitis B virus can persist in the host lifelong, predisposing the person to the development of significant and serious chronic sequelae.

Perinatal transmission, the transmission of infection from a gravid woman to her newborn, has been documented to result in a high rate of transfer of the HBV and may be the primary mechanism responsible for the high prevalence of this infection in high-risk third world populations. Most of these infections take place during birth or in the first few months of life. Data from Asia and Africa disclose that infants born to carrier mothers have a probability as high as 90% of acquiring the HBV from their mothers during the first year of life.[3] Once infected, these infants may continue to harbor the HBV for prolonged periods and, as a consequence, chronic active hepatitis, cirrhosis, or hepatocellular carcinoma may develop. The Centers for Disease Control (CDC) recently revised their recommendations regarding the routine screening of pregnant women for HBV to decrease the probability of neonatally acquired infection.[4,5]

Viral hepatitis was the third most common infectious disease (behind varicella and gonorrhea) reported to the CDC last year. The incidence of HBV infection in the United States appears to be increasing, with more than 25,000 cases of hepatitis B reported in 1984, a 25% increase from the previous five years.[6]

Virology

The hepatitis B virus is classified in the Hepadna group and is the only virus from this group that is known to affect humans. It has a propensity to infect and replicate in hepatocytes but appears to have no intrinsic cytopathic activity. The exact mechanism of hepatocyte destruction is not known, although evidence suggests that this process is mediated by the host immune system.[7] This explanation may partly account for the variation in the clinical presentation of HBV infection.

The intact viral particle—referred to as the Dane particle (Figure 1)—has been identified in the serum of patients with acute and chronic hepatitis B viral infections. It consists of a 42-nm outer shell known as the hepatitis B surface antigen (HBsAg) and an inner shell known as the hepatitis B core antigen (HBcAg), which houses the DNA. The DNA is double stranded and contains 3,200 kilobases. A soluble extractable protein, the hepatitis B e antigen (HBeAg), is thought to be a subunit of the HBcAg and is used as a marker for a highly infective state. Chimpanzee data, although not directly applicable to humans, suggest that serum containing both the HBsAg and the HBeAg is 10^8 times more infective than serum that is positive for HBsAg and anti-HBe.[8] Pure HBsAg, formerly known as the Australian antigen or hepatitis-associated antigen, is noninfectious. Inoculation of an immune-competent host with pure HBsAg can elicit a specific antibody response that is highly successful in protecting a person from a subsequent clinical infection.[9,10]

Epidemiology

Worldwide an estimated 200 million people make up the total pool of ongoing carriers of HBV. Considerable geo-

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
HBcAg = hepatitis B core antigen
HBeAg = hepatitis B e antigen
HBIG = hepatitis B immune globulin
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
Ig = immunoglobulin

graphic variability in the prevalence of the HBV carrier state exists from a high of 5% to 15% in Alaskan Eskimo and Asian populations to less than 0.5% in the general population of the United States.

The hepatitis B virus has been documented to be transmitted through exposure to body fluids and through parenteral routes. Blood transfusions, needle-stick injuries, and the use of contaminated needles or syringes have resulted in its transmission. Besides perinatal transmission, other nonparenteral spread, usually through close, intimate, or sexual contact, has also been associated with the spread of this virus.[11]

Numerous factors have been shown to predict the outcome of transmission in adults and children, including the presence of HBeAg, the age of a newly infected host, the immune status of the newly infected host, and the site and route of inoculation.[12]

Clinical Course of Infection

In a typical case scenario, acute hepatitis B infection in pregnancy does not appear to portend a more aggressive clinical course as was previously thought. Acute infection in the first or second trimester is rarely transmitted to the newborn if clinical resolution occurs before labor begins.[13] This infection, however, may pose a more substantial danger to the newborn if the acute stage occurs in the third trimester; 60% of these women will transmit the infection to the at-risk infant.[14]

The incubation period for acute HBV infection varies from 45 to 150 days. In healthy adults and children, only 50% of infections with HBV are manifested by clinical signs and symptoms; thus, most infections go unrecognized. Infants infected during the first year of life are more likely to be asymptomatic. When the infection does result in symptoms, the course of acute hepatitis is characterized by anorexia, nausea, malaise, weakness, and abdominal pain. The usual clinical signs are jaundice, icterus, hepatic tenderness, and weight loss. This acute infection will usually run its course in three to four weeks, but symptoms may be present for as long as six months. If the clinical course is prolonged beyond six months, then the acute infection has progressed into a chronic state. Typically this chronic state may persist for months to years and occasionally lasts for life.

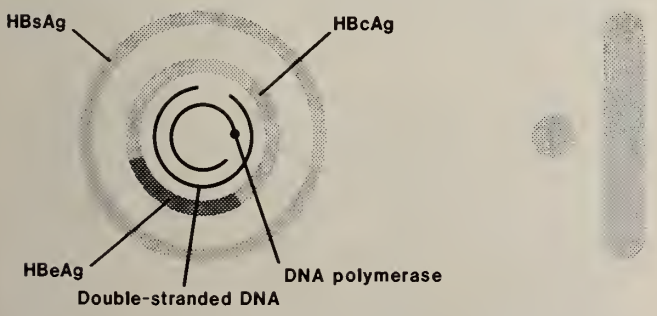

Figure 1.—On the left is a representation of an intact hepatitis B viral particle. On the right, two polymeric forms of the hepatitis B surface antigen (HBsAg) are represented consisting of HBsAg only in 22-nm spherical and cylindrical forms. HBcAg = hepatitis B core antigen, HBeAg = hepatitis B extractable antigen, DNA polymerase, and viral DNA

Fulminant hepatitis, the most dreaded form of clinical hepatitis, occurs in a small percentage of patients with acute hepatitis and is characterized by acute liver failure with hepatic encephalopathy and coma. About 70% to 80% of patients in whom fulminant hepatitis develops will die. The serologic markers in fulminant hepatitis are similar to those in typical acute hepatitis, although recent data suggest that viral replication and HBeAg production may actually be diminished in patients with fulminant HBV hepatitis.[15] In addition, several reports have demonstrated coinfection of HBV with the delta hepatitis virus in some cases of fulminant hepatitis.[16]

Serology of Infection

The first serologic marker to appear in acute HBV hepatitis is the HBsAg, which is present before the clinical onset of symptoms (Figure 1). Shortly thereafter, aminotransferase levels begin to rise and may reach peaks 20 to 100 times normal. At about the same time as the appearance of HBsAg, HBeAg may be detected in the serum. The HBeAg disappears before clinical symptoms resolve and is typically followed by the appearance of antibody to the HBeAg (anti-HBe). This seroconversion from HBeAg to anti-HBe suggests that the acute stage of the infection is resolving. Anti-HBs usually is detectable in the serum after the clinical symptoms have resolved and during the convalescent phase. Anti-HBs is usually not present until the HBsAg has disappeared such that in about 50% of symptomatic patients, a "window" period exists between the disappearance of HBsAg and the appearance of anti-HBs. High titers of anti-HBs can be construed as an indication of immunity.

Antibody to the core antigen (anti-HBc) can usually be detected early in the incubation period of acute HBV infection. This antibody consists of a mixture of both immunoglobulin (Ig) G and IgM and can persist in the serum for long periods of time. In adults, the IgM component can be present for as long as a year after acute infection.[17] The IgG component usually persists for many years and may persist lifelong. The presence of anti-HBc IgM during the window period has been accepted as presumptive evidence of a recent HBV infection. The hepatitis B core antigen is currently not a useful clinical marker since even in cases of acute hepatitis, it is usually not present in the serum in sufficient quantities to justify routine assay.[18]

Chronic infection with HBV can be characterized by two overlapping clinical scenarios, an asymptomatic carrier state and a chronic symptomatic hepatitis (Figure 2).[19] The "healthy" carrier state is characterized by a lack of symptoms and usually normal serum aminotransferase levels but with the serologic presence of the surface antigen (HBsAg). Persons with these signs usually have no detectable evidence of HBV replication or circulating virus particles, and liver biopsies in these patients are typically normal or show minimal changes.[20,21] Essentially all of these patients will show serologic evidence of anti-HBc primarily of the IgG class.

The symptomatic carrier state is similar to the healthy carrier state serologically but differs in that patients who are symptomatic have constant or intermittent elevation of

serum aminotransferase values and presumptive biochemical evidence of continued liver inflammation (Figure 3). Many of these patients have symptoms that wax and wane. A liver biopsy in patients with symptomatic chronic liver disease can reveal chronic persistent, chronic active, and chronic lobular hepatitis as well as cirrhosis or hepatocellular carcinoma. Evidence to date indicates that persons in the chronic carrier state will lose serum positivity to HBsAg at a rate of 1% to 2% per year.[22]

High-Risk Groups

Table 1 shows the high-risk groups for HBV infection and the estimated size of each group in the US population.[4,23]

Evidence for Perinatal Transmission

Stokes, Wolman, and co-workers in 1951 investigated several reports of newborn infants in whom signs of viral hepatitis developed within the first two months of life. They speculated that perinatal infection from an asymptomatic mother who harbored the "serum hepatitis" virus could be responsible for this perinatal transmission.[24] Three years later, Stokes and associates confirmed the presence of the serum hepatitis virus in the asymptomatic mother of one infant infected during the perinatal period by injecting serum from the mother and the infant into healthy volunteers.[25]

In 1970, Schweitzer and Spears reported that out of four mothers manifesting acute HBV infection during delivery or immediately postpartum, hepatitis developed in three of the infants who had serologic evidence of HBsAg.[26] Numerous other studies followed, predominantly from Asia, that showed that the HBV could be transmitted from infected asymptomatic mothers to their infants.[27-29] In these studies, infants who contracted perinatal HBV infections were frequently asymptomatic. The highest risk infants, those born of mothers with HBeAg-positive serum, have an incidence of perinatal infection as high as 85% to 95%.[3,29]

Although the exact mechanism of neonatal infection is not known, it is postulated that most perinatal infections occur at birth. Hepatitis B surface antigen tends to appear in an infant's blood at 3 to 4 months of age, consistent with infection occurring during the birthing process. The presence of HBsAg in the cord blood, however, originally thought to be associated with a high probability of infection, has been poorly correlated with the subsequent occurrence of the carrier state.[29,30]

The presence of maternal HBeAg has been shown to predict a high likelihood of perinatal transmission because it seems to correlate with the presence of high titers of viral DNA in the blood. If the mother is HBsAg-positive but HBeAg and antibody to HBe are absent in the maternal serum, the risk of infection to the neonate is approximately 31%. If HBeAg is absent but anti-HBe is present, the risk falls to approximately 10%.[29,31] Cases of fulminant hepatitis, however, have been reported to occur in infants born to women in the lower risk group, prompting the CDC and other experts to recommend that prophylaxis in these infants be instituted.[32-34] Studies in the United States suggest that

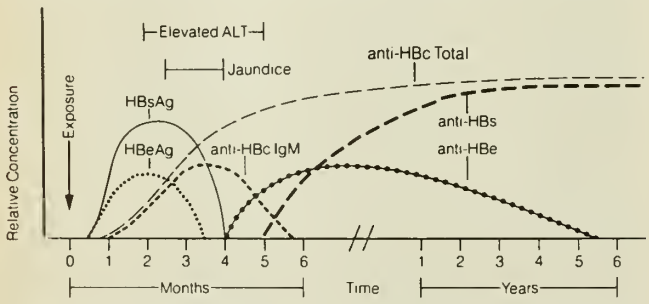

Figure 2.—The typical course of acute hepatitis B virus infection shows a characteristic elevation in serum alanine aminotransferase (ALT) levels preceded by the presence of hepatitis B surface and e antigens (HBsAg and HBeAg) in serum with clearing of both antigens before 6 months and the presence of antibody to hepatitis B core antigen (anti-HBc), anti-HBs, and anti-HBe in the convalescent phase (adapted with permission from Hoofnagle[19]).

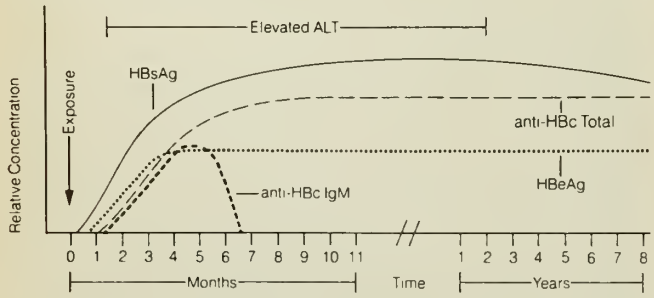

Figure 3.—The typical course of chronic hepatitis B virus infection is shown, with greater than 6 months of elevated serum alanine aminotransferase (ALT) levels and a persistence of hepatitis B surface antigen (HBsAg) without detectable antibody (adapted with permission from Hoofnagle[19]). anti-HBc = antibody to hepatitis B core antigen, HBeAg = hepatitis B e antigen, IgM = immunoglobulin M

TABLE 1.—*Estimated Prevalence of Hepatitis B Carriers in Selected Populations*

Population	*Prevalence, Percent*	*Estimated Total Number of Carriers*
Asian-Americans*	8-15	480,000
Alaskan Eskimos*	14	6,720
Subsaharan Africans*	6-14	4,400
Pacific Islanders*	5-10	20,800
Haitians*	7	6,510
United States population*	0.2	1,000,000
Intravenous drug addicts†‡	7	52,500
Institutionalized for mental retardation†‡	7	9,800
Medical personnel†‡	1	23,000
Centers for Disease Control highest risk§ group‡	7	604,000
Centers for Disease Control recommended screening group‡	4	755,000

*Data adapted from US Census Bureau, 1980.
†Adapted with permission from Krugman.[23]
‡From the Centers for Disease Control.[4]
§These are the recommended screening groups with greater than 7% prevalence.

TABLE 2.—*Prevalence of Hepatitis B Surface Antigen and Hepatitis B e Antigen Positivity in Selected Prenatal Populations*

Location	*Total Women Screened, No.*	*Positive for HBsAg, No. (%)*	*Positive for HBeAG, No. (%)*	*Percent Positive for HBe/HBs, %*
New York City*	472	18 (3.8)	6 (1.3)	33
Oakland, Calif†	484	49 (10.0)	18 (10.0)	37
United States‡	18,842	1,639 (8.7)	565 (3.0)	34

*From Friedman et al.[35]
†From Klontz.[36]
‡From Stevens et al.[37] This was a multicenter study: New York, San Francisco, and Los Angeles.

approximately 30% of HBsAg-positive pregnant women also possess the HBeAg (Table 2).[35-37]

Although about 5% of cases of vertical transmission are thought to occur transplacentally, the exact mechanisms leading to fetal infection are unclear. Whether prepartum microabruptions or direct invasion of the virus through an intact placental barrier is responsible for the subsequent intrauterine infection is still open to debate.[38]

The possibility that breast-feeding plays a role in perinatal transmission has been postulated after studies have shown breast milk of infected mothers to contain the antigen.[39] Current evidence, however, does not support the hypothesis that the virus can be transmitted through breast milk.[40]

Consequences of Neonatal HBV Infection

The presence of nonfatal acute neonatal hepatitis in eight Greek infants born of mothers found to harbor the Australian antigen prompted the consideration that certain maternal factors could be used to predict acute neonatal hepatitis.[41] Reports of acute fatal neonatal HBV hepatitis later helped to fuel the need to identify those factors that could successfully predict maternal transmission.[42] Although the presence of anti-HBe in HBsAg-positive carrier mothers was found to predict a low likelihood of transmission to the neonate, when transmission did occur, acute hepatitis developed in some of these infants, occasionally leading to death.[32-34]

The association of chronic HBV infection with the development of known sequelae—chronic active hepatitis, chronic persistent hepatitis, cirrhosis, and primary hepatocellular carcinoma—has been confirmed by a substantial body of evidence.[43] Sherlock and colleagues first described the association between the presence of HBsAg and primary hepatocellular carcinoma in 1970.[44] With the availability of a more sensitive radioimmunoassay for the detection of HBsAg, reports have surfaced that link higher rates of serologic evidence of HBV infection in patients with diagnosed hepatocellular carcinoma. Data from Africa and Asia have shown that 40% to 80% of patients with this cancer are also positive for HBsAg.[45] Epidemiologic and geographic data have shown that areas of high prevalence of HBsAg are also identified as concurrently manifesting a high prevalence of documented cases of hepatocellular carcinoma.[46] Furthermore, a case-control study from Senegal has shown the increased presence of HBV markers in the serum of mothers of patients with hepatocellular carcinoma, leading to speculation that viral transmission may be responsible for the development of the liver cancer.[47] Perhaps the strongest evidence as to the causal association between active HBV infection and the development of liver cancer stems from the work of Beasley and associates. More than 22,000 Taiwanese male government employees were observed for the development of hepatocellular carcinoma over 4½ years in this study.[45] More than 3,400 (15.2%) were found to be carriers of HBV, and these HBsAg-positive men had a higher rate of liver cancer than their HBsAg-negative cohorts (a relative risk of 94).[45,48] Using death registry data, this same group has estimated that the lifetime risk of death from hepatocellular carcinoma or cirrhosis or both is 40% to 50% for a male Chinese HBsAg carrier. Several reports have documented primary hepatocellular carcinoma occurring in HBsAg-positive children as young as 4 and 5 years old.[49,50]

The finding of HBV DNA integrated into the DNA of primary hepatocellular tumor cells has led to the speculation that viral DNA integration may be the initial event leading to the oncogenic transformation of infected hepatocytes. Hybridization techniques and Southern blot analysis have consistently shown the presence of hepatitis B viral genome sequences in some human hepatocellular carcinoma cells.[51-53]

Prophylactic Immunization Recommendations

High-titer anti-HBs was used in the mid-1970s to treat four newborns of mothers with acute HBV infection and appeared to successfully prevent HBV transmission to these infants.[54]

In 1981 data from an investigation in Taiwan showed a 75% efficacy in reducing the rate of HBV carriers in infants born to HBsAg- and HBeAg-positive mothers in a controlled trial of multiple doses of hepatitis B immune globulin (HBIG).[55] This was followed by a report from the same group of a randomized controlled trial using a revised schedule of HBIG and a plasma-derived hepatitis B vaccine that showed a 90% efficacy rate.[56] A similar trial in Hong Kong reported a 96% efficacy rate.[57] Stevens and coworkers, in a multicenter trial in the United States that observed 113 infants immunized using a similar protocol, found an 85% reduction in the expected carrier rate.[37] These same investigators revised the immunization protocol in a similar study of 122 infants receiving the new recombinant HBV vaccine and found a greater than 90% level of protection.[58]

The Advisory Committee on Immunization Practices of the CDC has recently revised its previous recommendation and now urges that all pregnant women be screened during a prenatal visit for the presence of HBsAg, preferably early in pregnancy when blood specimens for routine laboratory tests are drawn.[5] On the other hand, if the patient population contains a significant number of pregnant women at risk for contracting the HBV during pregnancy, the screening test may be delayed until the 32nd to the 36th week of gestation. In addition, as soon as an HBsAg-positive pregnant woman presents in labor, the obstetrical and neonatal staff should be advised of the HBV status of the patient so that appropriate precautions are observed. Newborn infants of these mothers should be immunized as soon as possible after birth once the

TABLE 3.—*Routine Pediatric Vaccination Schedule and Hepatitis B Virus (HBV) Prophylaxis for Infants of Mothers Positive for the Hepatitis B Surface Antigen (HBsAg)*

Age, months	*Hepatitis B Prevention Schedule*		*HBV Marker Screening*	*Routine Pediatric Schedule*
Birth	HBIG*	HB vaccine†	...	...
1		HB vaccine	...	...
2		...	...	DPT,‡ polio
4		...	...	DPT, polio
6		HB vaccine	HBsAg test§	DPT
12-15		...	HBsAG and anti-HBs test‖	...
15		...	...	MMR,¶ DPT, polio

*Hepatitis B immune globulin, 0.5 ml given intramuscularly within 12 hours of birth.
†Hepatitis B vaccine, 0.5 ml given intramuscularly within 12 hours of birth.
‡Diphtheria and tetanus toxoids and pertussis vaccine adsorbed
§Optional. If positive, indicates infection, and a third hepatitis B vaccine need not be given.
‖A test positive for HBsAg indicates therapeutic failure. A test positive for antibodies to HBsAg (anti-HBs) indicates therapeutic success
¶Measles, mumps, and rubella virus vaccine, live.

infant's condition is stable. Routine isolation of the infant is not necessary once the infant's condition is stable and all maternal blood is washed off. The newborn need not be isolated from the mother, but caution regarding maternal lochia should be exercised.

The accepted routine neonatal immunization schedule (Table 3) uses HBIG, 0.5 ml given intramuscularly, and hepatitis B vaccine and either recombinant (5 grams per dose) or plasma-derived hepatitis B vaccine (10 grams per dose), both preferably within 12 hours of birth. Both the HBIG and the hepatitis B vaccine can be given at the same time at different sites with no documented decrease in efficacy. The HBIG should be administered within 48 hours because delay in administration has been shown to result in a decreased protection of the newborn.[59] The vaccine may be given as long as seven days later if it is not immediately available. The hepatitis B vaccination is then repeated at 1 month and 6 months. No further HBIG is indicated. The vaccine can be given with the routine childhood disease immunizations with no decrease in their efficacy. A test of immunization success may be done at 12 to 15 months using HBsAg and anti-HBs, the absence of HBsAg and the presence of anti-HBs implying successful immunization.

If HBsAg screening has not been carried out by the time the mother is in labor or if test results are not available, then HBsAg screening should be done at the time of hospital admission or as soon as possible to ensure that the at-risk infant receives the recommended immunizations in a timely manner. If the hospital facility does not have the availability of HBsAg test results within a 48-hour period, strong consideration should be given to routinely administering HBIG to infants born of very-high-risk mothers—Asians, Haitians, Subsaharan Africans born outside the US, Alaskan Eskimos, and intravenous drug abusers. Several factors are important in considering the empiric therapy under these circumstances. The HBV carrier rate in these very-high-risk women may be as high as 15% and averages about 7% (see Table 1). In addition, the administration of HBIG after 48 hours has been found to result in a greatly diminished protection.[59] Both HBIG and hepatitis B vaccines have been found to be remarkably safe, with local mild reactions being the most commonly reported side effects. Finally, there is currently no proven antiviral therapy that has been shown to be efficacious in eradicating chronic HBV infection. Thus, routine administration while awaiting maternal HBsAg test results is justified in this setting to protect infants who would otherwise become HBV carriers. Once the HBsAg test results are available, then the decision for subsequent vaccine doses can be made.

If the infant was not identified as high risk antenatally but is the product of a high-risk mother and is older than 1 month, then the infant should be screened for the presence of HBsAg at the initial visit. If the HBsAg is absent, then the infant should be treated with HBIG and hepatitis B vaccines as soon as possible with repeat doses of vaccine at one and six months following the original vaccination (Table 3). Most investigators think that breast-feeding does not play a major role in the establishment of chronic HBV infections, particularly once an infant has been adequately immunized. Thus, little justification exists to discourage breast-feeding.

Although the CDC recommends that for screening purposes testing for HBsAg is sufficient, once the maternal serum is found positive for the HBsAg, then a thorough history and physical examination with evaluation of the liver function of the mother should be carried out to assess the potential for transmission and to detect occult acute or chronic hepatitis. Other immediate family and sexual contacts of the identified carrier should be evaluated for the presence of past or current HBV infection and to evaluate their candidacy for the hepatitis B vaccine.

The hepatitis B vaccine available in the United States is derived from pooled plasma of hepatitis B carriers and purified by a three-step process that appears to eliminate other serious potential infectious agents. This vaccine appears to elicit a protective antibody response in a high percentage of recipients. In July 1986, a new yeast-derived vaccine formulation produced by recombinant DNA technology (Recombivax HB) was licensed by the Food and Drug Administration. A large multicenter trial carried out in the United States has shown that the use of the yeast-recombinant vaccine is as effective as the plasma-derived vaccine in preventing the HBV carrier state in at-risk infants.[58]

Both vaccines have been proved to be safe and effective in adults, children, and newborns. The HBIG, which is pooled from serum containing high titers of anti-HBs, has also been shown to be safe and effective in adults and newborns.[60]

Who Should Be Screened?

The previous recommendations from the CDC identified 11 categories of high-risk women for whom screening for HBV was originally recommended (Table 4). The experiences of several large metropolitan centers established that using these recommended criteria to select patients for HBsAg screening resulted in missing 33% to 67% of HBsAg-carrier pregnant women. Investigators from the University of Florida screened all pregnant women during the two-year period of 1983 to 1985 and found that the CDC's previous recommended screening criteria identified only 14 of 43 pregnant women with HBsAg in their serum.[61] The sensitivity was 50% to 60%, specificity 71% to 75%, and a predictive value of 11% to 19% of these same CDC-recommended screening criteria in identifying laboring women with evidence of HBV infection in a large Ohio hospital.[62] A similar study from Dade County, Florida, of more than 5,300 pregnant women found the sensitivity of the screening criteria to be only 47%.[63] A comparison of the cost-benefit of routine screening for HBsAg with routine screening for syphilis in a population of pregnant adolescents revealed

TABLE 4.—*Women for Whom Prenatal Hepatitis B Surface Antigen Screening Was Previously Recommended**

Women of Asian, Pacific Island, or Alaskan Eskimo descent, whether immigrant or United States born
Women born in Haiti or Subsaharan Africa
Women with histories of
Acute or chronic liver disease
Work or treatment in a hemodialysis unit
Work or residence in an institution for the mentally retarded
Rejection as a blood donor
Blood transfusion on repeated occasions
Frequent occupational exposure to blood in medical or dental settings
Household contact with a hepatitis B virus carrier or hemodialysis patient
Multiple episodes of venereal disease
Percutaneous use of illicit drugs

*From Centers for Disease Control.[4]

comparable costs in case identification.[64] Finally, a decision analysis comparing the direct and indirect costs of a routine prenatal screening and newborn immunization program in the United States was shown to be cost-effective.[65]

After delivery, close follow-up of the mother is recommended, although specific guidelines for surveillance have not been agreed on. Because no proven therapy exists to resolve chronic HBV infection, efforts surrounding therapy for these persons are currently directed at the early detection of and early therapy for hepatocellular carcinoma. Preliminary results using α-fetoprotein screening in HBsAg-positive patients in China, South Africa, and Alaskan Eskimos have shown promise, particularly when used in combination with ultrasound evaluation of the liver.[48,66]

Summary

Routine screening of all pregnant women during the prenatal period has been shown to result in more effective and efficient means of identifying infants at risk for becoming long-term HBV carriers. Long-term sequelae of chronic liver disease can be averted if those infants born to positive mothers are immunized using a schedule of hepatitis B vaccine and HBIG at birth with follow-up hepatitis B immunizations. Standard precautionary measures should be taken during labor for those women found to carry the HBV, but isolating the infant and segregating from the mother need not take place. Breast-feeding need not be discouraged. Routine testing of the infant to determine immunization success should be done at 12 to 18 months. Close surveillance of the mother with frequent follow-up visits to look for evidence of chronic sequelae should be instituted.

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Medical Progress

Ununited Lower Limb Fractures

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Nonunion is a fairly common complication of fracture management, with an overall rate of about 3% for the skeleton as a whole and 9% for the tibia. High-energy injury fractures have a nonunion rate as high as 75%. Other factors that may lead to nonunion are inappropriate treatment, infection, and preexisting disease.

The diagnosis of nonunion is based largely on clinical examination. Plain radiographs and tomograms, computed tomograms, and contrast imaging may be used to confirm nonhealing. Radionuclide imaging can help determine the presence of infection, an impaired blood supply, or impaired osteogenic activity at the fracture site.

The treatment of ununited fractures is based on the principles of good fracture management: adequate immobilization, asepsis and soft tissue cover, osteoconduction (bone contact), osteoinduction (stimulation of bone growth), and metabolic well-being. New modalities for osteoinduction are promising adjuncts to standard treatment, the autogenous bone graft, but conclusive proof of efficacy in humans does not yet exist.

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Fracture nonunion is a relatively common problem faced by orthopedic surgeons. A nonunion is defined as a fracture that shows no radiographic or clinical evidence of healing over a specified time period. The time period when a fracture is considered a nonunion depends on the bone involved and the expected healing time for fractures of that particular bone. There are two basic types of nonunion. In a fibrous nonunion, fibrous tissue has grown across the fracture site but does not provide sufficient stability for function. In the second type, a synovial pseudarthrosis—a false joint with its own synovial lining—develops.

In the lower limb, nonunion can occur in any bone but most commonly occurs in the tibia and, to a lesser extent, the femur.[1] In this discussion we will concentrate on the diagnosis and treatment of tibial and femoral nonunions, although the principles apply to nonunions in general.

The overall rate of nonunion for the skeleton has been estimated at 3%.[2] In the tibia, however, the nonunion rate is much higher, having been reported to be as high as 9% for unselected cases[3] and 75% for displaced, open, comminuted fractures.[4] One of the major determining factors in the development of nonunion is the degree of soft tissue injury and interruption of osseous blood supply at the time of the initial injury. High-energy injuries can often lead to nonunion because of the degree of soft tissue damage. Thus patients who sustain lower extremity fractures as a result of motor vehicle accidents and, most commonly, motorcycle accidents are at risk for having nonunion. In an ongoing review of cases of nonunion at our institution, about 60% of tibial nonunions occurred in fractures that resulted from motor vehicle accidents, with most of those being motorcycle accidents. Similarly, 30 of 39 patients in a study by Gershuni and Pinsker were injured as a result of a motor vehicle accident.[5] Other populations at risk include the elderly and patients with an impaired ability to heal caused by metabolic or nutritional deficiencies. In this review, we will discuss the diagnosis, pathogenesis, and treatment of fracture nonunion in the lower limb.

Causes and Pathogenesis

The basic cause of an ununited fracture is the injury that produced the fracture. Fractures that are open, involve extensive soft tissue trauma, and involve bone loss or segmentation all carry a high risk of impaired union.[6] In general, these fractures result from situations with high-energy dissipation such as motor vehicle accidents or falls from a height.

Other factors that may have a causal relationship to nonunions are the treatment method, infection, and preexisting disease.[7] Open procedures for the internal fixation of closed fractures may inhibit healing by further devitalizing the bone, distracting the fragments, or getting them infected. Treatment methods that provide insufficient stability may inhibit union, and uncontrolled infection will devitalize tissue with a similar result.

Diseases that may decrease the rate of union fall into three major categories: metabolic or endocrine, congenital, and psychiatric, including chemical dependency.[8] Metabolic and endocrine diseases known to retard bone formation include diabetes mellitus, thyroid disease, parathyroid disease, rickets and osteomalacia, estrogen deficiency, Cushing's disease, Paget's disease, renal disease, and malabsorption syndromes. Congenital syndromes such as mucopolysaccharidoses and some dysplasias may cause delayed healing. Patients with psychiatric disorders often have difficulty complying with any treatment program; and chemical substances such as alcohol, tobacco, other street drugs, heparin, corti-

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costeroids, and anticoagulants may retard healing directly or through an associated nutritional deficiency.

The pathogenesis of nonunion can in most cases be related to one or more of the following six factors: bony instability, a lack of bone contact, impaired osteogenesis, an insufficient blood supply, poor nutrition, and infection. The importance of identifying the pathogenic factors for each case will become apparent in the discussion of treatment.

If gross motion is allowed at a fracture site, a true pseudarthrosis may form. Small amounts of motion, such as might occur in a well-applied plaster cast, can actually stimulate fracture healing; but if motion exceeds the strain limits of the healing tissue, it will be disrupted, inhibiting union. Those fractures close to joints are at particular risk for nonunion because they are difficult to immobilize, especially if the joint is stiff and all motion is translated to the fracture site.

Bone apposition is important for fracture healing. Cases in which apposition is not maintained, in which there is segmental bone loss, and where soft tissue is interposed between bone ends will probably proceed to an established nonunion.[9]

Patients with diseases or metabolic problems that retard osteogenesis, such as diabetes, can expect delayed union and should be cautioned that their chance of nonunion is relatively high. The stimulation of osteogenesis might be considered earlier in this group of patients than in those in whom normal healing responses are expected.

Dead bone does not heal well. If large amounts of bone are devitalized during the injury or if vascular disease is present, revascularization and healing will proceed slowly, if at all. The rate of nonunion is extremely high in such cases.

Nutritional deficiency, whether from a primary disease or inadequate intake, has a profound effect on healing in general, and fractures are not exempt. While calcium deficiency probably does not have a great effect on fracture healing, protein plays an important role. A nutritional assessment is a routine part of our evaluation of patients with delayed fracture healing.

Diagnosis

The diagnosis of fracture nonunion is based on a combination of clinical and radiographic findings. The clinical hallmark of nonunion in a lower extremity is persistent pain at the fracture site that is aggravated by weight bearing. On physical examination, gross motion of the fracture site confirms the diagnosis of nonunion. Often, however, an examiner must rely on more subtle findings because a nonunion can exist in the absence of gross motion. For example, a fracture that has been instrumented with orthopedic hardware can be stable on examination without bony union. In addition, fibrous tissue can grow across a fracture site and provide sufficient stability to make motion difficult or impossible to detect by examination. Other clinical signs include tenderness to palpation and pain with stress testing. To do a stress test, the examiner grasps the limb on either side of the fracture site and applies stress to the fracture. If this maneuver elicits discomfort, the examiner should expect incomplete bone healing. Some authors also claim that a decrease in sound transmission can be detected across the fracture site in a nonunion by placing a tuning fork at one end of the fracture and a stethoscope at the other,[10] and others have used strain gauges to measure fracture stiffness.[11]

The next step in the diagnosis of nonunion is the plain radiograph. Radiographs must be taken in at least two planes—anteroposterior and lateral—and oblique views are often helpful. These radiographs will help delineate the type of nonunion present. In a hypertrophic nonunion, abundant callus is present, but it fails to bridge the fracture gap. In an atrophic nonunion, there is an absence of callus formation. The bone ends are sclerotic appearing, and the medullary canals are obliterated, with a persistent wide gap at the fracture site.

Even with plain radiographs, the status of healing can be difficult to assess (Figure 1). Several other procedures have been used in this situation. These include plain tomography, computed tomography (CT), osteomedullography, and radionuclide scanning. Because plain radiographs are a two-dimensional image of a three-dimensional object, there may be apparent osseous bridging where none exists. This is especially the case in spiral fractures in which bony overlap can appear to represent healing. Both tomograms and CT scans can make it easier to assess such cases, providing three-dimensional information.

Osteomedullography is a little-used but potentially valuable diagnostic technique. To do this test, dye is injected into the medullary canal of the metaphysis distal to the fracture site. A tourniquet is inflated at the fracture site, and the extremity is imaged under fluoroscopy. In a positive test, evidence of vascular continuity across the fracture site is seen. A positive test indicates that the fracture will most likely heal without surgical intervention, but it does not correlate with the rapidity of healing.[12]

Radionuclide scanning has been recommended to delineate physiologic from pathophysiologic healing. Results have been mixed. Scans using technetium Tc 99m methylene diphosphenate have shown the presence of a synovial pseudarthrosis.[13] In addition, some authors have used radionuclide scans to determine whether the fracture has the biologic

Figure 1.—The radiophotograph shows a tibial nonunion. Note the callus apparently filling the fracture gap. Tomograms revealed the absence of a bony bridge.

ability to respond to a specific therapy such as electrical stimulation. With mature nonunions, radionuclide scans can identify large hypovascular areas that have no potential for healing. In such cases, operative intervention is needed.

In a case of nonunion, the possibility of infection must be considered. An increase in activity at the fracture site on the radionuclide scan is consistent with both bony healing and infection. Infection at the fracture site can also be a cause of persistent pain and contribute to the nonunion. Scans using leukocytes tagged with indium 111 may help differentiate subclinical osteomyelitis in these cases.[14]

Treatment

Principles

The treatment of ununited fractures generally follows the principles of basic fracture care: providing adequate mechanical stability in a satisfactory biologic environment. Those factors mentioned previously that are responsible for the creation of the nonunion, once identified, are modified to allow healing to proceed. Pathogenic factors invariably cause deficiency in one or more of the following treatment principles:

- Adequate immobilization
- Asepsis and adequate soft tissue cover (blood supply)
- Osteoconduction
- Osteoinduction
- Metabolic, including nutritional, well-being.

Immobilization

Adequate immobilization is that which provides sufficient bony stability to allow vascular invasion and soft tissue metaplasia within the nonunion. In some cases, stabilization alone can promote union. Depending on the fracture type, stability may be achieved best by external or internal methods. Nonunions that are inherently stable generally require limited immobilization provided by a cast, splint, or orthosis. This external method has the advantage of being noninvasive but the disadvantage of immobilizing adjacent joints, with residual stiffness and prolonged rehabilitation.

External fixation, a semi-invasive technique using pins placed into bone percutaneously and clamped to an external frame, can provide excellent stability.[15] Various frame types and configurations are available. Some allow compression, distraction, or axial loading at the fracture site. Advantages of this method include skeletal fixation, adjustability, and soft tissue access. Disadvantages include surgical risks, expense, a possibility of pin tract infection, and the necessity for removal. Early results using an external fixation technique developed by Ilizarov and co-workers in Siberia for cases involving bone loss or infection are encouraging.[16] This device uses fine percutaneous wires under tension attached to a complex frame that not only provides stability but also may be used to move and lengthen bone fragments. This technique is currently available at only a few centers in the western states.

Internal fixation of a fracture or nonunion is a third method of achieving stability and reduction. Pins, screws, plates, intramedullary devices, or a combination are used in a variety of constructs that vary from very flexible, with little inherent stability, to very secure, allowing full function including weight bearing. Pins and screws are generally flexible, while plates, depending on the type and fracture construct, are less flexible. Intramedullary devices are at the more secure end of the spectrum. Although all methods have relative advantages, the ultimate goal of invasive stabilization is to provide satisfactory alignment with fixation sufficient to allow full function. Pins and screws alone require limited surgical exposure, reducing injury to the blood supply, and will control alignment but usually require adjunctive external immobilization to protect the fixation. Plates can produce excellent stability and alignment but require extensive soft tissue dissection and clearly produce avascular areas adjacent to and under the plate. A plate can also prevent fracture ends from impacting and, if rigid, shield the bone from normal stresses that influence strength and remodeling. Intramedullary nails generally provide excellent stability and allow fracture impaction with the transmission of load through the healing bone, augmenting remodeling (Figure 2).[17,18] Intramedullary devices, however, destroy all or part of the endosteal blood supply of the bone shaft that, in a normal bone, accounts for about two thirds of the total supply. The use of these devices in a nonunion often prolongs healing. Implanting metal devices, because of the associated devascularization, is not recommended with a preexisting infection.

Asepsis and Soft Tissue Cover

With a high percentage of nonunions coming from open fractures and fractures with extensive soft tissue trauma, infection and a marginal blood supply are present in correspondingly high numbers. If present, infection must be treated with thorough debridement and aggressive local care.[19] Antibiotics administered through a tube or continuous irrigation systems may be more useful than parenteral antibiotics because of poor vascularity. Resecting infected bone is desirable in terms of curing the infection but may not be possible without leaving large bony defects that require long

Figure 2.—A femoral nonunion is treated with intramedullary stabilization. An implantable bone growth stimulator is seen distally.

and complex procedures for reconstruction. A subacute or chronic infection in a bone showing nonunion may be made quiescent with aggressive local care, allowing the treatment to proceed largely as in an uninfected case. When the infection cannot be controlled and all attempts at achieving union have failed, amputation should be considered. We have had many patients, disabled by an infected nonunion, who were able to get on with their lives and to be productive members of society following amputation. Although amputation should be mentioned as a treatment and a possible end result of the treatment of a complex nonunion, it should never be seriously considered until the patient has thoroughly weighed the alternatives, is completely familiar with the procedure, and requests it.

If soft tissue loss is present, the blood supply to the healing area is severely impaired. Covering exposed bone at the site of nonunion with well-vascularized soft tissue will assist the treatment of infection and maximize the chances of healing. With relatively small wounds where a healthy bed of granulation tissue can be produced with aggressive local care, healing by secondary intention—which can take a long time—or split-thickness skin grafting may be all that is needed. With larger tissue defects, coverage is achieved with local pedicle muscle flaps or free vascularized musculocutaneous transfers.[20] Nearly all large medical centers now have the capability of doing free vascularized tissue transfer, and no comprehensive treatment program for nonunion should be without this option.

Osteoconduction

To heal, a fracture must have a scaffold that new bone can use to bridge and heal the gap between bone ends. In normal fracture healing, the scaffolding is usually provided by the fracture callus or direct bony apposition. No scaffolding is present in a nonunion, so it must be provided. Osteoconduction is the term used for this purely mechanical scaffolding. Fractures with bony defects larger than half the diameter of the bone often lose osteoconduction and become nonunions because the callus cannot "jump the gap."

The most straightforward way of augmenting osteoconduction is to ensure direct bony contact by axial loading of the nonunion with weight bearing or compression using a fixation device. This step alone may promote healing. In cases where bony apposition is not possible, a scaffolding may be provided by interposing a bone graft or synthetic biocompatible materials such as hydroxyapatite or porous ceramics.[21] While all of these materials provide osteoconduction, only bone grafts have biologic activity.

Osteoinduction

Osteoinduction is defined as biologic stimulation that causes bone to form. If all previously discussed treatment principles are followed and union does not occur, osteoinduction should follow.

At present the only clinically proved method to stimulate bone formation, the so-called gold standard, is grafting with autogenous bone.[4,21,22] The results of all other techniques must be compared with those of autogenous bone grafting in controlled human trials. Thus far, no other technique has been shown to equal or better this method. Boyd and associates reported 262 cases of nonunion of the tibial shaft, 65% of which resulted from open fractures, treated with autogenous cancellous bone grafts.[1] After the initial grafting, 88% healed. Additional grafting improved the success rate to 93%. Nonunion in their series took, on average, about nine months to heal after grafting. Autogenous grafting with cancellous bone from the iliac crest remains our initial treatment of choice for most cases of nonunion.

For patients with nonunion with large bone defects, free vascularized autogenous bone grafts, often with adjoining soft tissue transfer, are a consideration.[23,24] Sources of bone for these transfers include fibula, iliac crest, and rib. Although these grafts tend to heal well, long periods of time are required for them to remodel to sufficiently withstand the large loads in the lower limb. Stress fractures through the graft can develop during this time.

In those patients who require repeated grafts, sources of autogenous bone may disappear. Allograft bone, now readily available from many sources, is an alternative. Although the biologic activity of allograft relative to autograft bone has not been confirmed, evidence is mounting that the stimulation is comparable.[22] Allograft bone is available in fresh frozen and freeze-dried forms. Irradiation or ethylene oxide is sometimes used to enhance sterility, and all material and donors are rigorously tested for infection. Despite the precautions, the use of allograft bone still has the disadvantage of a risk of biologic and chemical contamination and of reaction to foreign tissue. Advantages are that maximum amounts of bone can always be used and graft donor site morbidity—pain, infection, soft tissue damage—is eliminated.

Records of the electrical stimulation of fracture healing exist as early as the 19th century. In 1841 Harthsorne reported on the use of electricity in the treatment of pseudarthrosis.[25] Garrett in 1866 claimed success in the treatment of nonunion by applying a direct current at the fracture site through gold needles.[26] In 1953 Yasuda published a report on the relationship between electricity and bone formation, noting that a current passed through bone elicited new bone formation in the area of the cathode.[27] Becker and colleagues confirmed this work, showing that bone when stressed had an electrical potential proportional to the applied stress and that bone under compression was electronegative while the opposite was true for bone under tension.[28] On the basis of these findings, Bassett and co-workers implanted direct current devices in dog femurs and found bone formation around the negative electrode.[29] Many other investigators have shown the effect of small electrical currents on osteogenesis.

Reports of the electrical stimulation of bone grew rapidly. The majority, using a variety of electrical techniques, were encouraging.[30] Of 119 articles reviewed by Spadaro, only 6 described negative or equivocal results.[31] Brighton summarized the findings of these reports as follows:

- Electrically induced osteogenesis shows a dose-response curve in which current levels of less than 5 μA delivered through a cathode do not produce osteogenesis, current levels of 5 to 20 μA produce progressively increasing amounts of bone formation, and currents of greater than 20 μA begin to cause cellular necrosis;
- Electricity can accelerate fracture healing in laboratory animals;
- Given the proper criteria, electricity can induce bone formation in the absence of trauma;
- The reaction at the cathode results in oxygen consumption and hydroxyl radical formation; and
- Constant direct current is more effective in producing bone than pulsed direct current.[32]

Three types of electrical stimulation are available. The first involves the direct stimulation of tissue through electrodes that are either percutaneously inserted or implanted through a surgical incision. The second method was developed as an alternative to surgical implantation and involves the use of electromagnetic fields applied externally through coils strapped to the limb. The third is also noninvasive and uses a sinusoidal electrical field applied through electrodes attached to the skin. Paterson and associates reported 86% healing in a series of 47 patients with delayed union and 37 with nonunion using one to three implants of a direct current stimulator.[33] In a series of our patients with nonunion treated with the implantable stimulator, 68% healed after one implant and 87% healed with two or three implants. Bassett and colleagues reported a series of 127 patients with tibial nonunions treated with pulsed electromagnetic fields with a healing rate of 81%.[34] Other authors report healing rates of 64% to 71% using this method,[35] and 68% healed in our series. Brighton and Pollack, using the electrical fields, cite a 77% success rate in healing cases of nonunion.[36] We have no experience with this method.

At our center, electrical stimulation is reserved for those patients in whom adequate bone grafting procedures have failed or who have a contraindication to grafting. In recalcitrant cases, an implantable stimulator is sometimes used in conjunction with a bone graft (Figure 2), recognizing that a second surgical procedure will be necessary in 6 to 12 months to remove the current generator. In patients who refuse surgical treatment, cannot tolerate an operation for medical reasons, or whose local skin condition substantially increases the risk of complications, pulsing electromagnetic field stimulation is used. Compliance is essential and must be considered when choosing patients for this method. Noninvasive electrical stimulation with a fracture gap of greater than 5 mm or with a synovial pseudarthrosis has a poor success rate.

Mechanical stimulation methods to heal nonunions are probably effective, although evidence is still inconclusive. The earliest, and perhaps most convincing, method of mechanical stimulation is repetitive axial loading, such as weight bearing.[37] In the presence of adequate bending stability, weight bearing appears to accelerate the fracture healing process if impaction and load transfer through the bone is allowed, such as in a walking cast. That this same process will induce healing of a nonunion is implied but not yet proved. Early reports of mechanical stimulation through ultrasound claim success but have not been verified.[38]

Urist and co-workers have succeeded in purifying a protein from bovine bone that stimulates bone formation, bone morphogenic protein.[39] Studies of this substance carried out in animals are encouraging; as availability increases, it may become a viable alternative to autogenous bone grafting.

Metabolic Well-Being

The final intervention we can provide is metabolic. Adequate caloric intake, especially of protein, is absolutely essential for adequate fracture healing.[40] Mineral intake is less critical but should meet the minimum daily requirements. More than half of our patients with nonunions have had dietary deficiencies, making nutritional analysis and augmentation an integral part of the treatment program.

Chemical dependency often leads to nutritional deficiency and must be addressed as well. Medications that retard bone formation and healing should be eliminated if possible. These include corticosteroids, nonsteroidal anti-inflammatory drugs, anticoagulants, chelating agents, and heparin.

Summary

Nonunion is a common complication of fracture management in the lower limb, especially of those fractures that result from high-energy trauma such as motorcycle accidents. A knowledge of the pathogenesis of this complication aids in the diagnosis and treatment. Although increasingly sophisticated diagnostic modalities are becoming available, none have yet replaced a clinical examination for assessing fracture union.

The best treatment of nonunion is prevention. Good fracture management coupled with early recognition and rectification, if possible, of those factors that retard healing will minimize the likelihood of the complication. When nonunion does occur, the basic criteria of adequate stability, asepsis and an adequate blood supply, osteoconduction, osteoinduction, and metabolic well-being must be met. Optimum management dictates that it be individually tailored to each case. Autogenous bone grafting remains the procedure of choice for stimulating bone growth, although stimulation by electrical means or other bioactive materials may, in some cases, be useful adjuncts or even alternatives.

The final message is the one too often ignored: do not neglect the nutritional status of the patient. No treatment, even the most sophisticated, can replace the body's innate ability to heal itself given sufficient raw materials.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Asthma, and What You Can Do About It

Milton Millman, MD. Tidal Press, PO Box 1969, San Diego, CA 92112, 1988. 204 pages.

The author states that "patients and the general public usually lack sufficient medical information about asthma to judge whether or not they are getting the best treatment currently available." He attempts to provide the missing information in a language readily understandable by those with limited medical knowledge. Dr Millman, with associates Frank Millman, Ira Goldstein, William Grundon, and Alex Mercandetti, has produced a book that is as easy to understand as possible, with simplified explanations. This is done in four parts: Introduction to Asthma and Allergy; Diagnosis; Treatment; and Methods for Avoiding Allergens; along with a glossary and references. The book is written primarily for patients, parents of children who have allergies, and others who must work with this subject on a day-to-day basis. The 19 chapters contain numerous easily understood illustrations.

Asthma, and What You Can Do About It is not designed to be a self-treatment manual but is to serve as a home reference that would enhance the instructions and information provided by the treating physician. Of particular help is the section on environmental control of allergens. In the next edition of this book, Dr Millman should emphasize important rehabilitation factors such as summer camps and physical exercise programs for asthmatics, as well as information concerning asthmatics in the school system.

My own patients and I think that this book is quite suitable for the asthmatic patient and his or her family. Its proper use can serve to help prevent the need for hospital stays when the information provided is coordinated with the recommendations of the private physician. This book contains much information that when properly studied will allow the reader to understand that there is more to asthma than is realized by most physicians or the general public.

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Epitomes

Important Advances in Clinical Medicine

Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in orthopedics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

The Impingement Syndrome and the Rotator Cuff

THE ROTATOR CUFF MUSCLES are important stabilizers of the glenohumeral joint and provide a watertight joint space that maintains normal synovial fluid mechanics for cartilage nutrition. Rotator cuff disease is common in two distinct populations. It more commonly occurs in persons older than 35 years who have impingement with progressive supraspinatus degeneration and eventual tearing. The other population usually affected is athletes, aged 18 to 35 years, who do repetitive overhead activities. With continued overuse, their shoulders may become unstable and begin to sublux anteriorly, which can result in secondary impingement of the rotator cuff.

The roles of subluxation and secondary impingement have not been previously appreciated in the evolution of rotator cuff disease in young athletes. When the arm is continually abducted and externally rotated, stress is placed on the static stabilizers of the shoulder—the inferior and middle glenohumeral ligaments, anterior and posterior labrum, and anterior capsule. With repetitive stress, these structures may stretch or break down, allowing instability and eventual silent subluxation. This subluxation produces impingement of the rotator cuff against the coracoacromial arch, and the athlete will begin to have pain. Thus instability and impingement are not separate disorders but elements on a continuum of shoulder disease starting from overuse during overhead activity and progressing to microtrauma, anterior instability, silent subluxation, and, finally, painful impingement of the rotator cuff against the coracoacromial arch.

Patients with shoulder pain can be divided into four groups: Group 1 consists of patients with isolated episodes of impingement (older patients). Group 2 comprises patients who sustain repeated microtrauma from overhead activities, with primary instability and secondary impingement (younger athletes). Group 3 patients are similar to those in group 2 with the addition of hyperlaxity. Finally, group 4 patients have pure instability, usually following a major traumatic event, with symptomatic recurrent subluxation episodes.

The treatment of all groups begins with avoiding overhead activities, using anti-inflammatory medication, and strengthening the rotator cuff and scapular rotators. If not improved after three months, group 1 patients may benefit from decompressing the impingement with an acromioplasty. Group 2 patients require a more specific rehabilitation program that attempts to retrain the rotator cuff to fire in proper synchrony and that emphasizes strengthening of the scapular rotators (kinesiologic repair). If not improved after three months, these patients may require anterior surgical stabilization, with an attempt to minimize postoperative external rotation loss. An acromioplasty may worsen symptoms because the primary problem of instability has not been addressed. Group 3 treatment is similar to that in group 2, with postoperative rehabilitation modified by increasing the period of restricted motion. Group 4 patients usually do not improve with rehabilitation and usually require surgical stabilization for improvement.

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Tibial Fracture Update

TIBIAL FRACTURES that are closed and mechanically stable are best treated by a long-leg cast. Unstable and open tibial fractures often benefit from surgical treatment, especially in a patient with extensive injuries. Nonreamed intramedullary nails are the most common choice of orthopedic trauma surgeons for both open and closed unstable fractures. Recent studies indicate that the use of nonreamed intramedullary nails compares favorably with external fixation for grades 1 and 2 compound fractures, and their use avoids some of the complications of external fixation such as delayed union and pin tract infections. External fixation remains the treatment of choice for grade 3 compound fractures. Introducing the interlocking tibial nail allows for the control of length and rotation in complex fractures. Delayed union or nonunion is treated by early bone grafting using a posterolateral ap-

proach. Bone marrow and hydroxyapatite are being investigated as substitutes for bone grafts.

The high-energy open tibial fracture remains a difficult problem. The prompt recognition of vascular problems and early arterial repair with fasciotomies, stabilization with an external fixator, and early wound coverage using free or local flaps can lead to a more acceptable salvage rate. The anterior half-pin external fixator allows easy access to soft tissues and better nursing care. Severe crush injuries or severely damaged tibias with no posterior tibial nerve function and major muscle loss should be considered for early amputation.

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Diagnosing and Treating Chronic Distal Radioulnar Joint Pain

ULNAR WRIST PAIN HAS THE REPUTATION of being an extremely challenging clinical disorder. A careful clinical evaluation and standard x-ray films will sometimes fail to reveal the cause of the problem. In such situations, diagnosis and treatment can be aided by the newer techniques of the past several years—that is, scintigraphy, arthrography (sometimes in combination with fluoroscopy), computed tomography, arthroscopy, and magnetic resonance imaging.

Pain in the distal ulnar region can result from carpal lesions such as local arthritis or from pathologic disease of the triangular fibrocartilage complex (TFCC) or the radioulnar joint itself. A tear or peripheral detachment of the TFCC can be detected by wrist arthrography if dye is injected into the radiocarpal or distal radioulnar joint. An abnormality of the TFCC would be evidenced by an extrusion of dye across the complex. In elderly patients, this finding is not necessarily abnormal, so further investigation would be needed. The diagnosis can be confirmed by arthroscopy, which may also be used to debride a tear. Often tears in the TFCC can be observed noninvasively by magnetic resonance imaging, a technique that will undoubtedly be put to greater use in diagnosing wrist problems.

If the disease resides in the distal radioulnar joint itself, several treatment options are available. Ulnar shortening procedures are effective if the joint is intact but the ulna is simply longer than the radius. This increased ulnar variance often occurs as a result of a Colles' fracture. If the joint is also abnormal, other means of resolving the pain and improving forearm rotation must be sought. The Darrach procedure, long considered the mainstay of treatment of this type of problem, consists of resecting the distal ulna. Such resection, however, may fail to reduce the pain and, with excessive ulnar resection, may result in distal instability.

The importance of preserving the integrity of the ulnocarpal ligament complex has been emphasized. The reason for doing so is to maintain the TFCC and thus maintain stability of the ulnar side of the wrist. In response to this requirement, modifications of the Darrach procedure have been described. The hemiresection-interposition arthroplasty is one variation. Another is the matched ulna resection, wherein the distal ulna is partially resected so that the remaining segment parallels the contour of the distal radius and the stabilizing ligaments of the distal ulna are retained. Last, the Lauenstein procedure—sometimes called the Suave-Kapanji procedure—involves arthrodesis of the distal radioulnar joint along with resection of a 1- to 2-cm section of the distal ulna just proximal to the site of arthrodesis. This technique is effective in reducing pain and restoring forearm rotation while maintaining full support for the ulnar side of the carpus.

Thus far, no single procedure has been uniformly successful. The principles of treatment are yet to be fully elucidated and hinge on a broader understanding of structure and function. Until that point of understanding has been reached, this particular area of orthopedics will remain a focus of active clinical investigation.

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Diagnosing Internal Derangement of the Knee With Magnetic Resonance Imaging

INTERNAL DERANGEMENT OF THE KNEE represents a common medical problem with significant patient morbidity. Although arthroscopy has been used increasingly in the diagnosis—and treatment—of such derangements, less invasive diagnostic techniques can be used effectively before or in place of arthroscopy if they are accurate. In recent years, magnetic resonance (MR) imaging has proved to be a reliable method and, in many instances, has replaced arthrography in the evaluation of internal derangements of the knee. The advantages of MR imaging include excellent spatial and contrast resolution, direct multiplanar imaging capability, and the absence of a known biologic hazard.

Magnetic resonance imaging is particularly valuable in analyzing intra-articular soft tissue structures, including the menisci, cruciate and collateral ligaments, and the hyaline cartilage of the patella, the distal portion of the femur, and the proximal portion of the tibia. When done by experienced physicians, the accuracy of the MR examination in evaluating the menisci has been reported to be 90% to 95% (sensitivity 95%; specificity 91%). Similar accuracy has been evident in the diagnosis of cruciate ligament disruption. In these assessments, arthroscopy usually has been used as the gold standard, although it has been argued that owing to the ability of MR imaging to delineate intrameniscal alterations, some of the falsely abnormal MR results may, in reality, represent falsely normal arthroscopic examinations. As with any diagnostic examination, however, pitfalls in interpretation exist when the magnetic resonance study is done by persons who lack considerable experience and expertise.

Preliminary data also indicate that MR imaging holds great promise in the detection of focal or diffuse abnormalities of the articular cartilage in patients with osteoarthritis, osteochondritis dissecans, and chondromalacia patellae. The presence of a joint effusion is beneficial in the delineation of such chondral alterations, and, in the absence of joint fluid, some investigators have advocated introducing saline (or

gadolinium) before the MR examination (MR arthrography).

Kinematic MR examinations, in which a series of transaxial images are taken at various degrees of knee flexion, have been used to assess tracking abnormalities of the patellofemoral joint, providing new insight into patellar subluxation and dislocation.

The major disadvantages of MR imaging include its high cost and lack of availability. Recent technical advances using pulse sequences that tilt the net magnetic moment vector at an angle of less than 90 degrees allow the examination to be done in a shorter period of time with decreased cost; furthermore, with an increasing number of magnetic resonance installations in the United States and abroad, availability is becoming less of an issue.

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Treating Scoliosis

To determine the appropriate treatment of scoliosis, the natural history of the disease process must be understood. It is now known that in only a small percentage of skeletally immature patients curves less than 20 degrees will prove progressive. Factors that help to predict the risk of progression include the age of onset (the younger age has a higher risk); curve pattern (thoracic curves have the highest risk of progression); menstrual history (the risk of significant curve progression is three times higher for a premenarchal girl than a woman who is postmenarchal); the Risser sign of iliac apophyseal growth (risk is three times greater for Risser stage 2 or less than for a Risser stage greater than 2); and curve severity (risk of progression is about 20% for a 20-degree curve, 60% for a 30-degree curve, and 90% for a 50-degree curve).

The indications for nonoperative treatment have changed substantially in recent years based on this improved knowledge of the natural history. As it is now appreciated that most curves of less than 20 degrees do not progress, treatment is usually not recommended unless the curves are greater than 25 degrees or there is a progression of 10 degrees or more before treatment. As it is well documented that the risk of curve progression decreases dramatically after menarche, brace treatment would be started for few patients who have reached this stage.

The Milwaukee brace has been largely supplanted by thermoplastic thoracolumbar spinal orthoses that are form-fitting and easily concealed by clothing. Treatment protocols have traditionally required 23 hours per day until skeletal maturity is reached, followed by a gradual weaning program. Recent information indicates that part-time brace wear—16 hours per day—may be sufficient to arrest curve progression in many cases. As cosmetic appearance is not expected to improve with brace treatment, an unacceptable appearance contraindicates brace treatment.

Electrical stimulation of the convex side of the curvature has been tried both as an implanted system and by surface stimulation. Although some investigators disagree, the results of this method of treatment in several series have not shown any improvement over that expected by natural history alone.

The Harrington rod remains the gold standard of operative treatment. Instrumentation alone, however, is inadequate to preserve the correction, and a solid arthrodesis must always be obtained. Segmental fixation of the spinous processes to the Harrington rod may be accomplished using the Wisconsin wiring technique. Segmental fixation may also be accomplished using sublaminar wires attached to a rod placed on either side of the midline as described by Luque. Some series have reported an increase in neurologic morbidity from this procedure. Cotrel-Dubousset instrumentation is the most recent implant to become available. Its advantages include the ability to create both distractive and compressive forces on the same rod, to recreate thoracic kyphosis and lumbar lordosis, and to create fixation sufficiently stable that postoperative external immobilization is unnecessary.

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Magnetic Resonance Imaging in the Evaluation of Children's Spine Disorders

Back pain is uncommon in children and adolescents and deserves a thorough evaluation. A technetium bone scan remains the most useful test in localizing the source of nonspecific signs and symptoms or with a suggestion of infection. Magnetic resonance imaging (MRI), however, is the most definitive and cost-effective imaging technique for diagnosing and evaluating children's spine disorders not diagnosed by standard radiographs. Recent reports have documented MRI findings in cases of pediatric infection, neoplasia, and congenital vertebral anomalies. If a history, physical examination, and standard radiograph localize the problem, the MRI has proved helpful in further elucidating both pathologic anatomy and physiology.

The uncommon problem of pediatric spine infection has been an issue of primary disc space infection versus osteomyelitis with extension into the disc space. In osteomyelitis and neoplasia, T1-weighted images have shown decreased signal intensity within affected vertebral bodies. T2-weighted images often reveal sparing of the disc space with neoplasia and involvement of the disc with infection. A report of MRI scanning in a child with classic physical and plain radiographic findings of diskitis revealed (on T1-weighted images) osseous involvement above and below the narrow disc consistent with osteomyelitis. Likewise, a child's hamstring tightness, paravertebral spasm, and altered gait could be explained by the posterior herniation of a narrowed lumbar disc into the spinal canal, as noted on T2-weighted images. The noninvasive, nonionizing nature of MRI has offered new information on a historically self-limited condition in which invasive studies are usually not justified.

Congenital vertebral anomalies can involve both osseous

and neural elements, and invasive studies have been required to fully evaluate the onset and progression of pain, neurologic deficit, and deformity. Magnetic resonance imaging is useful in detailing spinal cord anomalies such as syringomyelia, tethered cord, diastematomyelia, and lipoma. Myelography remains the first choice where the three-dimensional change in patients with severe deformity prevents adequate MRI imaging.

A disadvantage of MRI is the potential need for sedation in a child reacting claustrophobically to the gantry and the intimidating sounds of the scanner. Metallic spinal implants, being nonmagnetic, do not present a danger, but they do distort the image throughout their length. Good resolution can usually be obtained above and below the level of the hardware. Magnetic resonance imaging has become a useful diagnostic tool and, with more experience, may offer new insights into the etiology and pathophysiology of children's spinal disorders.

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Fractures of the Distal Radius

ABOUT 80% OF ALL FRACTURES of the radius occur at the distal end of the bone. The goal of treatment is to restore the anatomic relationship of the distal end of the radius to the carpus (radiocarpal joint) and to the distal ulna (radioulnar joint). Fortunately, a typical Colles' fracture can be effectively treated by closed manipulation and stabilized with a well-molded above-the-elbow cast for five weeks. Slight palmar flexion and ulnar deviation of the wrist will maintain the reduction of the fracture, and extreme palmar flexion of the wrist is contraindicated.

If a fracture is unstable, or the fracture reduction cannot be maintained with a plaster cast, then external fixators have been effective in stabilizing fractures once they have been properly reduced. It is extremely important to understand that a poorly reduced fracture of the distal radius will not improve merely by applying an external fixator. The better the restoration of the bony and articular alignment of the radius, the better the end result after the fracture has healed.

High-velocity injuries of the distal radius that frequently occur in younger patients are difficult to treat. These fractures are often intra-articular, involving both the radiocarpal and distal radioulnar joints. Comminution is often another component of these fractures. Many of these intra-articular fractures in young adults are best treated by open reduction and internal fixation. The fractures can be stabilized by smooth Kirschner wires or a buttress compression plate. This seems to be the best method of restoring the anatomic relationships at the radiocarpal and distal radioulnar joints. Wrist arthroscopy may be a useful adjunct to examine the restored articular surface of the distal radius. A high incidence of posttraumatic arthritis at the radiocarpal joint has been found in younger patients in whom there is residual incongruity of the radiocarpal joint.

Despite our best efforts to properly treat fractures of the distal radius, almost a third of these fractures are associated with some complications, involving either bone or soft tissue. Some of these complications are transient, while others may require secondary reconstructive procedures.

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Administering Steroids in Unicameral Bone Cysts

UNICAMERAL BONE CYSTS are cystic, fluid-filled lesions that develop principally in the proximal humerus (70%) or proximal femur (25%) during childhood and adolescence. Pathologic fracture through the thin cortical wall is the usual event leading to diagnosis. To avoid repeated fractures with a resultant shortening or deformity is the main motivation for treating the cyst.

For several decades before 1975, the "standard" treatment for bone cysts consisted of curettage and bone grafting, either with banked bone or autologous iliac crest bone. The magnitude and morbidity of this procedure, coupled with a success rate of only 50% to 60% in obliterating the cyst, led to research on alternative treatments.

In 1973 Scaglietti of Florence found that the fluid obtained from bone cysts was chemically similar to edema fluid and the lining tissue contained scattered inflammatory cells. He began a clinical trial of injecting cysts with methylprednisolone acetate, a potent and relatively insoluble synthetic corticosteroid. When used in growing children, this treatment stimulated bone formation in the cyst cavity that either completely obliterated the cyst or produced sufficient healing that further fractures would not occur.

The cyst injection procedure is generally done with the patient under brief general anesthesia and is aided by image-intensified fluoroscopy. Large spinal needles or, when necessary, bone biopsy needles are drilled through the proximal and distal aspects of the cyst wall. While the lesion is viewed by fluoroscopy, the cyst is irrigated with diatrizoate meglumine (Renografin) or a similar contrast material by injecting through one needle and allowing the fluid to exit through the other. This confirms that the lesion is a bone cyst and that it is composed of a single chamber. If the lesion does not fill like a cyst, a biopsy, either open or by needle, should be done. If more than one chamber is identified, two needles should be placed into each chamber and each injected separately. The use of only one needle to inject a chamber causes an increase in the intraosseous pressure and considerable pain for one to two days. Once the chamber(s) is shown radiographically, methylprednisolone acetate (Depo-Medrol), 40 or 80 mg per ml, is injected, the total dose ranging from 40 to 200 mg depending on the cyst volume. The needles are withdrawn, and a pressure dressing is applied to the puncture sites.

If a prompt contrast venogram is produced, the likelihood of the cyst responding to the steroid injection is decreased because much of the steroid probably will leave the cyst cavity shortly after injection.

Because injection can lead to transient demineralization of the cyst wall, it is prudent to protect the involved bone from trauma for at least two months after injection. X-ray films are taken at two-month intervals. The maximum increase in density after a single injection typically occurs at four to five months, at which time a decision is made regarding the need for further injections. In 10% to 25% of cases, healing occurs with a single injection. The rest generally will heal with further injections (seldom more than four) either completely or sufficiently that the risk of further fracture is minimal.

In view of the high success rate, low morbidity, and relatively low cost, corticosteroid administration is generally the initial appropriate therapy for unicameral bone cysts in immature patients. Bone grafting should generally be reserved for cysts that fail to respond to multiple injections or cysts that present after physeal closure.

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Internal Fixation of Degenerative Disease of the Lumbar Spine

THE SURGICAL TREATMENT OF DEGENERATIVE DISEASE of the spine frequently involves both laminectomies and fusions. Attempts at fusion can result in nonunion. The incidence of nonunion increases when the number of levels involved in the fusion increases. Fusions of the lumbar spine are also done to correct deformities. These challenges have motivated the design of various devices for internal fixation.

Most designs of devices for internal fixation have incorporated instruments used in treating scoliosis. The two most common types have been the Harrington rod, a hook and distraction system, and the Luque system, which uses a metal rod with wires that are placed beneath the various laminae, pulled around the rod and then tightened. Although these systems have worked well in patients with thoracic scoliosis, neither of them has given solid fixation in the lumbar spine because it is more mobile and has greater ranges of motion than the thoracic spine.

There have been other systems adapted to the lumbar spine, such as Knodt rods, Weiss springs, and Luque rings, but none of these have produced secure fixation. The use of these systems may also result in a loss of lumbar lordosis, causing the patient to stand in a constantly flexed position. In 1976 a system of placing screws in the pedicle and attaching them to plates was developed in France. This provided rigid fixation in the lumbar spine.

Since then, numerous variations of the plate-and-screw or rod-and-screw system have been developed, permitting surgeons to secure fixation with control of spinal alignment. A number of complications may develop with these systems, however. There may be a pronounced increase in the infection rate, two to three times that of other surgical procedures, both because of the implant itself and because of the length of the operation. Broken screws and a loss of fixation can also occur. With some patients who have osteoporosis, it is difficult to gain good purchase with the screw, so the procedure must be done with caution. In addition, there may be an increased incidence of degeneration of the first mobile segment above the fusion because of stresses transferred by the rigidity of the fixation devices.

Because of the complications, these implants must be used selectively and with great caution by someone who is familiar with both spine surgery and the systems of internal fixation of the spine. Great care must be taken by those who embark on this to train adequately, both in the laboratory and in the operating room, before they do this procedure by themselves.

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The Management of Giant Cell Tumors of Bone

GIANT CELL TUMOR OF BONE is a benign neoplasm found typically in the end of long bones in patients in their third and fourth decades. The surgical treatment most commonly used over the past 20 years has been a conservative curettement of the lesion and packing of the defect with some form of bone graft material. Two years following this primary attack on the tumor, the recurrence rate has been about 30%. Because of this high failure rate, many surgeons in larger centers have taken a more aggressive approach to the problem by suggesting a wide resection of tumor including the adjacent joint surface. The large resulting defect is then replaced with an osteochondral allograft, total joint prosthesis, or an arthrodesis. Indeed, with this aggressive approach, the recurrence rate dropped to around 5% but at a high price of functional disability for the lifetime of a young patient with an excellent prognosis for a long life.

For the past decade a new approach has been taken to reduce the significant disability resulting from these more aggressive wide resections and at the same time keep in line with a 5% recurrence rate. This approach has been an aggressive curettement of the lesion followed by packing of the surgical defect with bone cement commonly used in total joint arthroplasty. The procedure is relatively simple compared with large bone grafting or prosthetic operative procedures, and the complication rate is low. Patients are allowed the early use of the involved joint because of the immediate stability provided by the cement replacement of even large surgical defects frequently created just beneath the joint surface. It must be emphasized that the curettement must be aggressive and supplemented by the use of high-speed dental burs and water-pick lavage of not only the bone defect but the surrounding soft tissues as well. In the few cases where recurrence has resulted, the problem can usually be handled by a simple local debridement of the recurrent area without removing the entire cement block and with minimal injury to the adjacent joint. Although long-term results are not yet available, at this time this procedure holds considerable promise for better results than previously achieved.

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Free Tissue Transfer in the Salvage of Traumatized Extremities

OPTIONS FOR RECONSTRUCTING massively traumatized extremities have increased dramatically over the past dozen years due primarily to the development of microsurgical techniques and the description of numerous free tissue-donor sites. Extensive bone and skin loss in an extremity is often compounded by crush injuries to vessels, nerves, and muscles. Free vascularized tissue transfers are one-stage procedures to provide distant site coverage, permitting surgeons to select a donor site that best meets the specific needs of a recipient site in order that form, contour, and function may be reconstructed.

Besides providing well-vascularized coverage to enhance healing and prevent infection, transferred tissue can include free cutaneous grafts that may be innervated to provide sensation, free muscle grafts that may be innervated to restore active motion, and vascularized bone that can effectively bridge large bony gaps. In some series, free tissue transfer has been successful in 80% to 90% of cases.

While initially reserved for delayed reconstruction, there now is a great interest in emergency free flap operations. In extensive traumatic defects, the immediate transfer of distant skin, muscle, or myocutaneous flaps may save injured structures from additional loss caused by desiccation, infection, and fibrosis. In Yugoslavia the flap failure rate, infection rate, bone healing time, and duration of hospital stay have been decreased in patients undergoing free tissue transfer within the first 72 hours of injury compared with those patients whose treatment was delayed. This experience needs to be duplicated in this country.

Whether immediate or delayed, free tissue transfer has become the treatment of choice for reconstructing massive soft tissue and bony defects. With the application of microsurgical techniques, many limbs that previously would have been amputated can now be salvaged.

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Editorials

Now That Health Care *Is* Worth Something

SHORTLY AFTER THE TURN OF THE CENTURY it was said that a person who sought help from a physician stood only a 50% chance of benefiting from the encounter. Even this may have been an improvement over the bleeding and purging that was customary in even earlier times. But this century has been one of almost geometric progress in medical science and the technology to apply this new knowledge to patient care. Particularly in the last several decades and during and since World War II, health care clearly has come to be worth something, and this has begun to have profound effects on such things as life expectancy and quality of life, especially for the chronically ill. This is also having profound effects on the delivery of health care.

If a product or a service is worth something in our society, then it would seem logical that its value should be convertible into dollars and its practical worth measured in terms of economic profit and loss or the bottom line on a financial statement. This is what has been happening to health care in this nation. "Nonprofit" is being replaced by "for profit," and economic goals are being substituted for what were mainly humanitarian goals in many aspects of the health care enterprise. Much of health care is becoming a business in the good old American tradition. This was recognized by a government that on the one hand encouraged and promoted competition in the delivery of health care, and on the other, activated regulatory and legal interventions to control any monopoly or restraint of trade by physicians or others in what was now looked upon as an industry. And it is not to be forgotten that a result has been that health care has become the most regulated industry in the nation.

It would seem that this way of looking at health care ignores what it is really all about. At its heart, health care is first a humanitarian and only second, a business enterprise. Health care is about people who get sick and who need help. It merges into prevention of illness in patients and others, and into quality of life and well-being for a citizenry that needs to work in a healthy place, live in a healthy community, and have a healthy environment. This is a far cry from the approach of what we think of as a profitable business where what is unprofitable is avoided or simply eliminated. And not surprising, when one thinks about it, it has already proved unprofitable to give health care to those who cannot pay, even if they need it. Unhappily this fiscal bottom line approach does not expose the equally real value or long-term profit to society of making health care available to economically disadvantaged children and youth. Even preventive services tend to be curtailed because their long-term value does not show on today's bottom line. It is already becoming all too clear that the economic laws of supply and demand, cost control through economic competition, and all the trappings of the marketplace will never reduce the cost and, worse, will inadequately meet humanitarian and societal needs for health care. Yet we seem to be hurtling down this blind alley at breakneck speed with no thought of looking where we are going, let alone of ever turning back.

The conventional wisdom of today is that health care has long since become too important to be left entirely to physicians, and this is probably true. There are many problems—individual patient and more generic health care problems—that require the help of others outside the profession if they are to be solved satisfactorily. But it is also essential that physicians and the medical profession participate more fully in decisions about societal interventions in health care, at whatever level. Health care *is* worth something. It is costly, but its real worth is its humanitarian value to the people who need it and to the society that needs medical expertise to help it provide a healthy environment for a healthy citizenry. Physicians and the medical profession work in the humanitarian heartland of health care, where the human problems are and where health care can make a difference. Physicians with their training and professional experience can help to point out what is wrong, what is likely to happen, and what can be done about it, wherever health problems appear. Yet physicians and the medical profession are often second guessed by nonprofessionals for what they do or do not do in their professional practices, and their professional experience and expertise are often passed over when political or economic decisions are made in health care.

The issue is a fundamental one, and it seems to focus on the meaning of worth. Is the worth of health care economic, measured in dollars to the payer or the provider, or is it humanitarian, measured in its value to the persons, the communities, or the society that need and use it? The dollar costs cannot be overlooked or ignored. Health care *is* worth something and it costs something, sometimes a lot, but the fundamentally humanitarian purpose of all health care should always be kept uppermost in mind. In the view of this writer, it is receiving far less attention than it should in many of the public and private facets of this huge industry or enterprise that affects so many people and so much of society as a whole.

MSMW

Tuberculosis and HIV Infection—New Opportunities for an Old Pathogen

TUBERCULOSIS is a historic disease that has been a major cause of human suffering and death for centuries. Though tuberculosis commands great interest for those who study the past,[1] its contemporary role in human health should not be underestimated. Despite dramatic declines in the prevalence of and mortality from tuberculosis observed over the past several centuries, tuberculosis remains a major clinical and public health problem. It is estimated that there are 16 million prevalent cases of tuberculosis in the world today, with 8 million new cases annually. While detection and treatment programs have an appreciable impact on the clinical course of tuberculosis in many nations, an estimated 3 million persons die of the disease each year.

Tuberculosis is a truly opportunistic disease. *Mycobacterium tuberculosis* exploits deficiencies in cellular immunity to cause disease in the young and old and in those with congenital or developed abnormalities of cellular immunocompetence. The transmission of *M tuberculosis* takes advantage of deficiencies in our social network. Tuberculosis is a continuing problem in prisons, among the homeless, in intravenous drug users, and in the poor, particularly poor

blacks and Hispanics. The control of tuberculosis is made difficult by the lag between the acquisition of infection with *M tuberculosis* and the development of disease, a process that may take many years. While asymptomatic persons with *M tuberculosis* infection are not likely to be contagious, once symptomatic pulmonary disease occurs, the opportunity for transmission is great until effective chemotherapy is instituted. A failure to promptly diagnose and treat tuberculosis invariably results in a transmission of the disease to previously uninfected persons.

The emergence of the dramatic epidemic of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) in the past decade has created new opportunities for *M tuberculosis.* Persons infected with HIV have profound deficits of CD4+ (helper) lymphocytes as the time from infection lengthens.[2] The eventual ablation of cellular immunocompetence that occurs in the majority of infected persons allows the clinical expression of opportunistic disease, previously held in check by a functioning immune system. Since the initial descriptions of *Pneumocystis carinii* pneumonia, mucocutaneous herpes simplex, and Kaposi's sarcoma in homosexual men, much attention has focused on the unusual opportunistic diseases found in patients with advanced HIV infection.

As the AIDS epidemic matures, however, major changes are being seen in both the persons in whom AIDS develops and the clinical manifestations of their AIDS-related illnesses. The proportion of AIDS cases resulting from intravenous (IV) drug use has grown from 14% before 1983 to 23% in 1988.[3] In some states, such as New York and New Jersey, more IV drug users than homosexual men are diagnosed with AIDS. Increases in the number of IV drug users with AIDS are accompanied by an increasing number of non-drug-using heterosexuals and children with AIDS whose risk for HIV infection is contact with an IV drug user. Racial and ethnic minorities are increasingly affected by AIDS, in part by the overrepresentation of IV drug users in AIDS cases. Thus, as AIDS enters the 1990s, it is becoming a disease of the urban poor, its transmission facilitated by the high prevalence of drug use endemic in large cities.

The clinical manifestations of HIV infection are also changing as the epidemic grows. The development of opportunistic diseases as immunosuppression progresses reflects the past exposures that a person has had to potentially opportunistic organisms. For reasons as yet unexplained, homosexual men have a peculiar predilection for Kaposi's sarcoma developing, though this expression of cellular immunodeficiency is undergoing a notable decline at this time.[4] *P carinii* appears to be endemic in developed countries, and pneumonia caused by this pathogen is the index diagnosis in approximately 60% of AIDS cases in the United States. In countries where infection with *Toxoplasma gondii* is highly prevalent, such as Haiti and France, cerebral toxoplasmosis is a common AIDS-related diagnosis. In many parts of the world, infection with *M tuberculosis* is prevalent and reactivation of this organism is becoming an important marker of HIV-induced immunodeficiency. In the United States, infection with *M tuberculosis,* as noted above, is more prevalent in ethnic minorities, IV drug users, prisoners, and the poor—groups emerging as having a higher prevalence of HIV infection than other segments of the population. Hence, tuberculosis is becoming an increasingly prevalent problem in persons with HIV infection and AIDS.

In this issue of the journal, Theuer thoroughly and lucidly reviews the importance of tuberculosis in patients with HIV infection. His discussion of the topic is particularly important for clinicians who provide care for persons who may be dually infected with HIV and *M tuberculosis.* Several points raised by Theuer deserve reiteration. First, HIV infection per se is not a risk factor for tuberculosis. Among persons with HIV infection, the risk of tuberculosis is greatest in those with a high likelihood of prior *M tuberculosis* infection. Therefore, the prevention of AIDS-related tuberculosis is dependent on diagnosing *M tuberculosis* infection (with a tuberculin skin test) before disease develops and giving preventive therapy. The efficacy of standard isoniazid prophylaxis in HIV-seropositive patients has not yet been proved, but prudence dictates that such therapy should be offered. A failure to provide prophylaxis to HIV-seropositive IV drug users with a positive tuberculin skin test was recently shown to result in a high incidence of subsequent tuberculosis.[5]

Second, while tuberculosis is likewise not a risk factor for HIV infection, a growing proportion of patients with tuberculosis are also infected with HIV. At the San Francisco Tuberculosis Clinic, almost 30% of adults with tuberculosis (excluding Asian immigrants) were seropositive for HIV in a recent study.[6] Similar studies in other areas where AIDS is prevalent have shown comparable results.[7] The diagnosis of tuberculosis should raise questions about patients' immunocompetence. Serologic testing for HIV, with appropriate counseling and consent, should be advised in patients with newly diagnosed tuberculosis.

Third, the clinical features of tuberculosis in patients with advanced HIV infection may be atypical. A high index of suspicion for tuberculosis must be maintained when patients with HIV infection present with constitutional or respiratory symptoms. Some clinical clues remain helpful. Adenopathy or cavitary lesions on a chest radiograph are strongly suggestive of tuberculosis in patients with or without HIV infection. The tuberculin skin test is positive in 40% to 80% of patients with HIV-related tuberculosis, depending on the stage of the HIV disease. Skin testing should be routinely done on all patients with HIV infection, particularly if symptoms are present. Clinical specimens from patients with HIV infection should always be stained and cultured for mycobacteria. When acid-fast bacilli are identified on a smear, therapy for tuberculosis should be initiated while awaiting culture results.

Finally, tuberculosis can be effectively treated with standard drugs in patients with HIV infection. Experience in treating AIDS-related tuberculosis is uniformly favorable, as patients respond comparably to non-HIV-infected tuberculosis patients. Resistance to isoniazid is no more commonly encountered in patients with HIV infection than in other populations. Adverse reactions to antituberculosis agents may be more common in patients with advanced HIV disease,[8] but most patients can successfully complete therapy. The optimal duration of the treatment of AIDS-related tuberculosis remains controversial.[9] The current recommendation of the Centers for Disease Control and the American Thoracic Society is to treat for at least six months following conversion of sputum cultures for patients with pulmonary disease.[10] The use of an organized treatment system for tuberculosis that ensures compliance and follow-up will greatly enhance treatment efforts. Physicians unfamiliar with tuberculosis therapy should refer patients with HIV-related

tuberculosis to public health authorities for therapy. Contact investigation by public health authorities can also help prevent tuberculosis in close associates of such patients.

The HIV epidemic has dramatically altered the practice of medicine in the past decade. Diseases that were rare before 1980, such as *P carinii* pneumonia and cryptococcal meningitis, are now commonplace. But as the epidemic continues to unfold, the greatest opportunist may prove to be *M tuberculosis.* The relative virulence of the organism compared with other AIDS-related opportunists and its high prevalence in populations with increasing risk of HIV infection may considerably delay consigning *M tuberculosis* to the history books.

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Fracture Nonunion

APPROXIMATELY 6 MILLION FRACTURES occur annually in the United States, and the associated cost to society is estimated at $18 billion per year.[1] About a third of the fractures occur in the lower extremities, and nonunion of such fractures results at the rate of 2% to 7%, although in complex injuries the failure of union is even more frequent. The significance of nonunion of lower extremity fractures to a patient in terms of pain, suffering, residual joint stiffness, decreased limb function, and economic loss can be great. A review of fracture nonunion by Csongradi and Maloney elsewhere in this issue is a timely reminder of the problem.

The basic reason for the development of nonunion of a fracture is not always apparent. Many fractures, of course, are complicated by significant bone loss, a diminished blood supply, or infection, which manifestly provoke a nonunion. The more subtle requirements, however, of type, degree, and time of immobilization and load bearing, if misapplied, also can result in a fracture failing to heal. Although a certain amount of motion at the fracture site is undoubtedly perceived by the periosteum as a stimulus to callus formation, too much motion for too long may result in a futile overproduction of new bone and the development of an "elephant foot" or hypertrophic pseudarthrosis. Alternatively, rigid immobilization of the fracture by internal fixation techniques may be imperative to facilitate healing of, for example, a femoral neck fracture. The lack of a cambium layer in the cervical periosteum demands endosteal or cortex-to-cortex repair, which appears not to tolerate significant micromotion. Thus, a fundamental problem in preventing the development of nonunion is to define the permissible required or lack of motion at a fracture site; further experimental and clinical research is clearly indicated to answer this question.

Watson-Jones found that any fracture immobilized for long enough would heal.[2(p22)] While this may be true, long-term immobilization in a cast is incompatible with the optimal restoration of limb function. Thus, if an experienced orthopaedic surgeon can decide within a few months or less from the time of injury that a fracture will not unite or will not do so within a reasonable further period of time, the change from cast immobilization to an alternative stimulus to fracture healing should be made. It is certainly not in the patient's best interest to arbitrarily wait 6 or 12 months in a plaster cast to confirm that little or no progress toward fracture union is occurring, especially as such lengthy periods of limb immobilization provoke substantial hard and soft tissue atrophy and joint stiffness.

The excellent care of fracture nonunion clearly demands the restitution of bone continuity, correction of deformity in all planes, maintenance or recovery of function, and no further complications from the treatment. All of these requirements should take place over a reasonable period of time. In the long bones of the lower extremity, these demands can frequently be met by intramedullary fixation with a reamed nail. It is preferable to do the procedure in a "closed" fashion that, although technically more demanding, generally lowers morbidity. The introduction of nails that are "locked" by screws traversing the tubular bone through fenestrations in the nail now has provided the capability for stable internal fixation of lower limb long bones almost from epiphysis to epiphysis. After nail insertion, the patient can frequently commence early weight bearing with no additional or supplementary external immobilization. When the time comes to remove the nail, the likelihood of refracture, which sometimes occurs after plate and screw removal, is greatly decreased.

The treatment of fracture nonunion by electrical stimulation alone fails to address a most basic need, that of the correction of deformity. Neither is the preservation of limb function enhanced by the requirement of bioelectrical techniques for a further period of cast immobilization (and frequently non-weight bearing) while healing is expected to progress. Electrical stimulation as a distinctly advantageous technique that stands on its own merits has not been substantiated by subjecting it to rigorous examination. The only prospective double-blind trial to examine the issue was done by Barker and co-workers in 1984.[3] Their results showed a slightly improved rate of success when the external coils applied to the casted tibias were *not* connected to the power source! Other studies have combined electrical methods with internal fixation, external fixation, or bone grafting—established methods that are known to frequently promote fracture repair—and thus confused the issue. The patients in most studies were selected to reject those with bone defects of more than 1 cm or greater than half the diameter of the bone, synovial pseudarthroses, and sometimes osteomyelitis at the fracture site. The science, or lack thereof, behind these reports is unconvincing. Notwithstanding this, piezoelec-

trical phenomena are clearly a part of cell biology, and further studies and sophistication of methods may yet produce valid applications for the treatment of ununited fractures. Until then, the perceived recent decreased interest in the clinical use of electricity in fracture management is understandable. Csongradi and Maloney reserve the method for those patients who have failed or are unsuitable for grafting procedures, or refuse the surgery.

Autogenous bone grafting remains the standard osteogenic stimulus for atrophic or defect nonunions. Such grafts have frequently been applied in an onlay manner in the tibia by a posterolateral approach. When no additional internal fixation has been used, cast immobilization is necessary in a limb that inevitably has already been subjected to long-term immobilization. While union rates are good, the functional end result has been poor after such an approach.[4] The posterolateral incision for bone grafting has been recommended, particularly for infected nonunions of the tibia. The technique, however, of a direct approach through the (frequent) soft tissue defect, radically debriding down to bleeding bone, and applying autogenous bone is simpler and produces excellent results. The purely cancellous bone used in this open (Papineau) technique is quickly revascularized and is resistant to infection. Allograft bone and hydroxyapatite or porous ceramic materials are being used in the surgical treatment of fracture nonunions and show promise, as Csongradi and Maloney have indicated. It is unwise to insert them into an actually or potentially infected environment, however.

Csongradi and Maloney mention a new technique of external skeletal fixation recently introduced into this country from Russia by Ilizarov and co-workers for use in situations of defect nonunions with or without infection.[5] The Ilizarov technique, developed by its originator in 1951, relies on the principle of compression-distraction whereby the ends of fracture fragments lying separated from each other are approximated and then compressed while at the same time slowly distracting at a distant corticotomy site. The nonunion is stimulated to heal while the corticotomy site, with its medullary blood supply intact, is slowly widened, during which new bone is formed in the gap. Atrophic nonunions with almost any degree of bone defect and infection are suitable cases, and adjunctive bone grafting is unnecessary. Many other variations of bone and also soft tissue transport are possible. It is hoped that the new technique will bring a further dimension to the management of difficult nonunion problems and correct deformity and shortening while maintaining function. It is a meticulous technique, however, and if poorly or inappropriately used, could fall into disrepute.

Some of the most difficult cases of nonunion to treat are in tibias with defects, infection, and a lack of soft tissue coverage, usually resulting from high-energy motor vehicle accidents. These problems invariably occur in young people, and the orthopaedic traumatologists' instincts are to reconstruct and save the limb. Indeed, with recent advances in microsurgical free tissue transfer, external and internal fixation techniques, and now the Ilizarov method, the possibilities of a successful outcome have improved considerably. Great care in patient selection for such salvage attempts is imperative, however. The implications of long and repeated hospital stays, pain and psychological upset, and the usual huge economic burden must be clearly understood by surgeon and patient. In many cases an informed decision to try to obtain a functional extremity over a maximum period of a year is a legitimate one. Otherwise, an early and equally informed decision to amputate should be made; such a solution can be constructive and most advantageous to all concerned.

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Case Reports

Central Cervical Spinal Cord Syndrome Due to Minor Hyperextension Injury

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THE CENTRAL CERVICAL SPINAL CORD SYNDROME is most commonly caused by a severe hyperextension injury of the neck. It is often associated with fracture or dislocation of the cervical spine, and considerable head injury is often present. Motor vehicle accidents are a common cause of this syndrome, especially high-speed crashes in which there is rapid deceleration, causing the occupants of the car to be thrust forward. When an occupant's head contacts the windshield or some other part of the automobile, the neck is violently hyperextended. These cases associated with substantial injury are usually recognized and diagnosed correctly. Often not appreciated, however, is that minor injuries to the frontal region of the head that seem insignificant at the time they occur or hyperextension of the neck in the absence of a head injury can also cause the central cord syndrome. In these cases there may be a delay in recognizing the presence of spinal cord damage.

A hyperextension injury to the spinal cord is especially likely to occur in patients with congenital shortening of the anteroposterior diameter of the spinal canal or if some pathologic process is present that decreases the space available for the spinal cord.

Three cases of a central cervical spinal cord syndrome due to a minor hyperextension injury are reported. Each one had preexisting compromise of the space available for the spinal cord due to a congenitally small spinal canal with a superimposed cervical spondylosis.

Report of Cases

Case 1

The patient, a 74-year-old woman, had persistent severe headache, neck pain, and weakness of her upper extremities. She had also noticed atrophy of the intrinsic muscles of the hands. She had difficulty crocheting or doing other activities that she had previously done with ease. These abnormalities followed a motor vehicle accident in which her vehicle was struck from the rear. Impaired function of the hands was observed within a few hours after the accident. She felt tingling of the shoulders and arms within a few minutes after the injury.

On neurologic examination a year after the injury, she had severe atrophy of the interosseus muscles of the hands with an impairment of function of her fingers. There was also some decreased strength of the other muscle groups in the upper extremities but no abnormality in the lower extremities. There was no sensory abnormality on examination, and no sphincter disturbance was present. X-ray films of the cervical spine showed moderately severe osteoarthritic changes with a 2- to 3-mm posterior subluxation of C-3 on C-4 and an anteroposterior spinal canal diameter of 12 to 13 mm.

Case 2

A 68-year-old woman presented with severe weakness of the upper extremities and mild weakness of the lower extremities. Her symptoms had developed the evening before while the patient was intoxicated. She tripped while getting into a car and bumped her forehead on the roof of the car, causing a small contusion of the forehead and hyperextension of the neck. On examination she had weakness that was greatest in the intrinsic muscles of the hands and the extensors of the wrists. Tendon reflexes were absent. There was flaccidity in the upper extremities, and there were Babinski's signs in the lower extremities. There was a mild decrease of pain and temperature sensation below the C-5 level. A myelogram showed a nearly complete spinal subarachnoid block due to cervical spondylosis from C-3 to C-7. Her condition improved gradually following an anterior diskectomy and interbody fusion.

Case 3

The patient, a 48-year-old woman with schizophrenia, was admitted to hospital with impaired function of all extremities. Her family suspected a medication overdose. The evening before admission she became angry, ran, and jumped face down on a bed, causing her neck to hyperextend when her head hit the pillow. Following that she was not able to get up on her feet without assistance, and she had urinary retention. The patient was initially hyporeflexic in all extremities and had bilateral Babinski's signs. She had severe weakness of the upper extremities. There was no significant sensory abnormality. X-ray films of the cervical spine showed severe degenerative changes with an anteroposterior diameter of 9 mm at the C5-6 level. A myelogram showed nearly complete block at this level. She had an anterior diskectomy and interbody fusion. She had gradual improvement but never regained good function of her upper extremities and could not walk without assistance.

Discussion

The central cervical cord syndrome is a constellation of neurologic symptoms that are due chiefly to damage in the central portion of the cord with relative sparing of peripheral pathways. It was described as a clinical disorder by Schneider and co-workers in 1954.[1] They reported eight cases and cited reports of several similar cases from the literature, some from the 19th century. They described the following triad:

(Peterson DI, Altman K: Central cervical spinal cord syndrome due to minor hyperextension injury. West J Med 1989 Jun; 150:691-694)

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- Motor impairment that is greater in the upper extremities than in the lower;
- Bladder dysfunction that usually consists of urinary retention;
- Variable sensory abnormality below the level of the lesion.

The motor abnormality in the upper extremities is chiefly lower motoneuron in type. It may consist of a decrease in tone and weakness, diminished deep tendon reflexes, and eventually atrophy that is usually most severe in the interosseus muscles. If the lower extremities are involved, they have an upper motoneuron impairment with spasticity, hyperreflexia, and Babinski's signs. In some cases the sphincter may not be impaired. The sensory abnormality when present may be dermatomal in distribution, and even if it is severe, there may be sacral sparing. There may be hyperpathia or burning paresthesias in the shoulders and arms.

A central cord syndrome due to minor hyperextension of the neck may completely resolve or, if there is residual impairment, it may be so mild as to consist of only weakness of the interosseus muscles of the hands followed by atrophy as in our first case, or it may produce permanent quadriparesis as in our third case. The wide range of severity of this syndrome may be partially responsible for its frequently being unrecognized when a patient is initially examined in an emergency department or by physicians in other settings, especially if there is no history of significant injury.

None of the patients in this report were recognized as having the central cord syndrome when they were initially examined by medical personnel. A delay in diagnosis may be due to the fact that this condition, although not rare, is sufficiently uncommon that many physicians are not aware of it. In some cases malingering is suspected because the abnormality is greater in the upper than in the lower extremities. Scher found there was a delay in the diagnosis in a third of cases of the central cord syndrome.[2] This delay in diagnosis is especially likely to occur in patients presenting without a history of substantial injury. Cases of obvious neck injury, especially if there is fracture or a dislocation, are less likely to be overlooked.

It is well established that the central cord syndrome may occur without evidence of bone injury.[3] It may also occur without any evidence of soft tissue damage to the neck or any head injury, as in our first and third cases. The central cord syndrome is usually caused by hyperextension, but other kinds of neck injury can also cause this condition.

The three cases in this report vary greatly in the severity of spinal cord damage and residual impairment of function, but they are all similar in that each one was associated with minor trauma that would not ordinarily be considered severe enough to cause spinal cord damage from hyperextension of the neck. These cases are also similar in that all of them had significant compromise of the space available for the spinal cord before the injury. One had a minor contusion on the forehead, but the other two had no external evidence of trauma.

Hyperextension of the neck may cause damage to the spinal cord by at least two mechanisms: First, buckling of the ligamentum flavum associated with hyperextension of the neck may compress the cord. It has been shown in cadavers[4] that hyperextension of the neck can result in a decrease in the anteroposterior diameter of the spinal canal by as much as 30%. The decrease in space available for the cord may be less in a living subject than in a cadaver because of resiliency of the soft tissues; nevertheless, a notable decrease in the size of the canal may occur. The second mechanism is a "pincher" effect[5] that may occur between the posterior elements of the vertebral column and the lamina of the vertebra below even without dislocation or fracture in a person with preexisting compromise of the spinal cord space (Figure 1). For this reason, acquired degenerative changes and congenital narrowing causing spinal stenosis in the cervical area predispose to central cord damage. These abnormalities that decrease the anteroposterior diameter of the spinal canal may be asymptomatic before hyperextension occurs.

Hyperextension injuries may be due to falls, motor vehicle accidents, sports injuries, assaults, direct blows to either the forehead or the back of the neck, or even hyperextension during intubation for anesthesia. This syndrome has also been reported after a cervical laminectomy, in which case it may be due to hypotension or vascular compromise.[6] One report cites some instances of minor trauma causing a central cord syndrome in children.[7] It occurred in a 2-year-old child who fell from a crib, and the only apparent injury was a forehead abrasion. Another occurred in a 7-year-old child who threw herself face down on the bed as our third patient did.

Damage to the spinal cord presenting as a central cervical spinal cord syndrome may be the result of any of several different types of pathologic processes or a combination. These injuries are thought to produce contusion of the spinal cord that may lead to small hemorrhages and necrosis.[8-10] Magnetic resonance (MR) imaging is the best method to show spinal cord damage in these patients. In some cases of

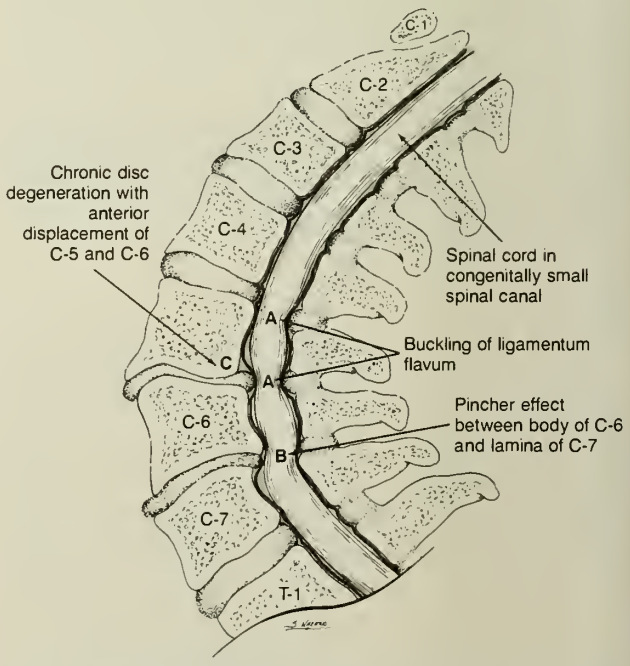

Figure 1.—A sagittal section through the spinal canal shows **(A)** buckling of the ligamentum flavum during hyperextension of the neck and **(B)** a "pincher" effect between the lower part of the C-6 vertebral body and the lamina of C-7. Spinal cord damage by these mechanisms is more likely if a congenital spinal stenosis and degenerative changes are present. **(C)** Degenerative changes, including thinning and protrusion of the intervertebral disc, and displacement of C-5 on C-6 make compression of the spinal cord during hyperextension of the neck more likely.

acute injury, edema can be shown by this procedure (Figure 2). True hematomyelia rarely occurs. Eventually there may be cyst formation appearing as an area of decreased density by MR imaging (Figure 3). It has been reported that in some cases ischemia of the spinal cord may occur, due either to anterior spinal artery damage or to injury to the vertebral arteries that may result in vasospasm.[10] Damage to the most medial anterior horn cells leads to a lower motoneuron abnormality, resulting in interosseus atrophy in the upper extremities. This is most likely due to contusion caused by direct compression of the spinal cord. It has been suggested that sensory pathways may be damaged in central areas of the cord as they decussate.[11] It has also been postulated that the laminated descending and ascending tracts in the spinal cord may be damaged more medially, thus accounting for preferential injury in the upper extremities compared with the lower extremities.[1] Anatomic evidence for this is poor, however.[11]

There is a report of a soccer player having an immediate loss of function of all four extremities from heading a ball during practice, but he had good recovery within a short time after the injury.[12] In cases of this kind, an acute concussive effect rather than contusion, hemorrhage, or infarction is the likely cause of a transient loss of function. In some cases, a delayed onset of symptoms has been reported.[7] A vascular disorder is more likely in these cases. In the three cases in this report, there is insufficient information about how soon symptoms began after the minor injury to say what the mechanism of injury was. It was likely that of direct compressive contusion of the cord, but damage to the spinal arteries also may have occurred.

Studies in animals have shown that compressive forces applied directly to the surface of the spinal cord will cause central hemorrhage and necrosis.[13] The size of the lesions is proportional to the force. Yamada and associates found that the oxidative metabolism was unchanged in the spinal cord of cats immediately after an impact injury when no structural damage occurred.[14] If more force is applied, hemorrhagic contusion results. Thus, there are apparently several mechanisms that produce the tissue damage and loss of function in the central cord syndrome, depending on the type and severity of the trauma.

The ratio of concussive effect, edema, hemorrhage, and necrosis is an important factor that determines the degree of recovery or severity of residual impairment. The impairment that is due to edema and that which is due to a transient loss of function caused by an acute concussive compression may resolve relatively well, but areas that are damaged by hemorrhage or infarction recover poorly.

Schneider and colleagues suggested that this syndrome had a good prognosis, and recovery usually occurred with conservative treatment.[1] This is not always the case.[15] Severe residual impairment is present even in some cases due to minor injury as in our third patient. If ongoing cord compression is present, surgical decompression may decrease symptoms and prevent further damage. Surgical treatment of the spinal cord is not likely to be beneficial even if hemorrhage is present.

The case histories in this report show that severe central cord syndrome can result from a minor hyperextension neck injury in patients who have a small spinal canal. One of the

Figure 2.—A magnetic resonance imaging scan of the cervical spine shows increased density in the spinal cord consistent with edema at the level of the C-3 and C-4 vertebrae **(arrow).** The scan was done with T2 weighting. This person was involved in a motorcycle accident and initially presented with severe weakness of the wrist extensors and interosseus muscles. He had a Babinski's sign on the left. Sensation was decreased below C-6 on the right. The patient had greater than minor injury to the neck because in this case there was a fracture of the body of C-5. This patient is not one of our three reported cases of only minor injury.

Figure 3.—Magnetic resonance imaging of the cervical spine and spinal cord shows an area of cyst formation at the C3-4 level nine months after an acute hyperextension injury. Disc herniation and spinal subarachnoid block were present at the time of injury so an anterior diskectomy and interbody fusion were done at C3-4. This patient sustained major injury in a motor vehicle accident.

most important factors in determining whether spinal cord damage occurs from a neck injury is the preexisting space available for the spinal cord and not necessarily the severity of the injury.[16]

The central cord syndrome should be considered in any patient with impaired extremity function after a head or neck injury even though the injury is a minor one and also in patients with impaired function of the extremities even if there is no history of head or neck injury.

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Mycotic Aneurysm Presenting as Fever of Unknown Origin

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FEVER OF UNKNOWN ORIGIN was defined by Petersdorf and Beeson in 1961 as fever present for at least three weeks without its cause being determined after a week in hospital and with reasonable investigations.[1] Mycotic aneurysms as a cause of fever of unknown origin are uncommon and are associated with a high mortality due to catastrophic rupture. Osler in 1885 first coined the term "mycotic aneurysm" to describe a mushroom-shaped aneurysm in a patient with infective endocarditis. It has since been used to describe all infective aneurysms except those due to syphilis. Despite all the latest investigative and therapeutic methods available, the diagnosis and early recognition of mycotic aneurysm remains difficult and the treatment continues to be associated with high mortality and morbidity rates. We report a case that clearly highlights the problems encountered in establishing an early diagnosis of mycotic aortic aneurysm as a cause of fever of unknown origin, especially in an elderly patient with prolonged nonspecific symptoms, an absence of localizing physical signs, and at an age when atherosclerotic aortic aneurysms are common.

(Asthana S, Walker D, Iyengar S, et al: Mycotic aneurysm presenting as fever of unknown origin. West J Med 1989 Jun; 150:694-696)

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Report of a Case

The patient, a 76-year-old retired farmer who had received a Bjork-Shiley mitral valve replacement in 1971 for rheumatic mitral stenosis, but who was otherwise well, presented to his family physician with a sudden onset of fever, rigors, and right acromioclavicular arthralgia. He was admitted to hospital and after receiving physiotherapy and analgesics, was discharged home on June 5, 1987, with resolution of the arthralgia but still febrile. On June 26, he was readmitted with fever, chills, anorexia, malaise, vague abdominal pains, myalgias, increasing ankle edema, occasional cough without expectoration, and a weight loss of 11 kg (25 lb). He received empiric therapy with gentamicin sulfate and cephalothin sodium given intravenously for two days and was transferred to University Hospital in Saskatoon. There was a history of an allergy to penicillin.

On physical examination on admission, he was slightly obese, fully conscious, and oriented, with an irregular pulse rate of 76 per minute, a blood pressure of 140/98 mm of mercury, respirations 18, and a temperature of 37.2°C (98.6°F). Other findings included bilateral pitting edema of the lower legs, a jugular venous pulse 2 cm above the sternal angle at 45 degrees, and the cardiac apex 3 cm to the left of the midclavicular line in the fifth intercostal space. A pansystolic apical murmur of grade II/VI and an aortic ejection

Figure 1.—An axial computed tomographic scan of the abdomen shows ring calcification in the intima of the abdominal aorta with surrounding soft tissue density anteriorly. No gas is present in the soft tissue mass nor is there adjacent bone destruction.

systolic murmur of grade II/VI were audible. All peripheral pulses were palpable. There were no abdominal masses, and the examination revealed no other abnormalities.

Initial laboratory investigations revealed a hemoglobin of 115 grams per liter, a leukocyte count of 24×10^9 per liter, platelet count 322×10^9 per liter, and a notably increased erythrocyte sedimentation rate of 112 mm per hour. The electrolytes, urea, creatinine, and serum aminotransferase values were all normal. A urinalysis revealed 10 erythrocytes and 10 leukocytes per high-power field with a trace of protein. There was cardiomegaly with pulmonary venous hypertension on a chest radiograph. Atrial fibrillation was confirmed by an electrocardiogram.

The patient remained febrile at 38°C to 39°C (100°F to 102°F) and had episodes of chills, anorexia, and episodic ill-defined lower abdominal pain with no new signs on several detailed physical examinations carried out during the hospital stay. An abdominal ultrasonogram done on admission was reported to be normal. The distal abdominal aorta was not visualized. A computed tomographic (CT) scan of the abdomen eight days after admission revealed a 4-cm distal abdominal aortic aneurysm with a 2-cm calcified ring within it (Figure 1). This was thought to be an unusual appearance for an atherosclerotic aneurysm, but the significance was unclear. Ten days after admission, 1 set of blood cultures out of 14 specimens collected showed a growth of *Streptococcus pneumoniae,* and he was treated with a regimen of intravenous gentamicin and vancomycin hydrochloride for a presumptive diagnosis of prosthetic valve endocarditis. This therapy was discontinued after three weeks due to deteriorating renal function, persistent fever ranging from 37.5°C to 38.5°C (99.5°F to 101.3°F), a lack of clinical improvement, and a fall of his hemoglobin level to 70 grams per liter with a leukocyte count of 19.9×10^9 per liter. The alkaline phosphatase level rose from 285 to 627 IU per liter, with the γ-glutamyl transferase value at 363 IU per liter. A subsequent workup during the five-week hospital stay that included fungal blood cultures; a urine culture; echocardiography; a liver biopsy; bone marrow aspiration, biopsy, and culture; serum complement levels; serologic tests for *Brucella* species and Q fever; a urine culture for cytomegalovirus; an upper gastrointestinal series; double-contrast barium enema; endoscopic retrograde cholangiopancreatography; an isotope liver and spleen scan; acid-fast bacilli culture and stains of bone marrow, liver, and sputum; and a temporal artery biopsy did not reveal any significant pathologic process. A total body scan using gallium Ga 67 citrate was done without any abnormality found. The ultrasonogram was repeated (Figure 2) and confirmed the presence of an aneurysm that was eccentric in configuration and suggested a leaking abdominal aneurysm or mycotic aneurysm. During the fifth week an angiogram was done because of the previous ultrasonographic and CT findings. At the time of the angiogram, no right common femoral pulse was palpable. An intra-arterial digital subtraction angiogram (Figure 3) done through the left common femoral artery showed a saccular aneurysm approximately 6 cm in diameter arising eccentrically from the distal abdominal aorta and involving the aortic bifurcation with occlusion of the right common iliac artery. The diagnosis of mycotic abdominal aortic aneurysm was made.

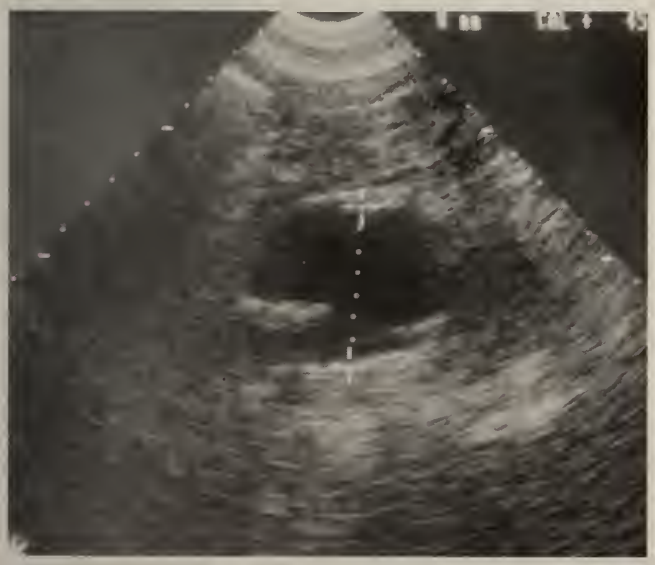

Figure 2.—A sagittal ultrasonogram shows the abdominal aorta posterior to an echo-free mass that communicates with the abdominal aorta at its lower end. The appearance is of a saccular aneurysm rather than the typical fusiform aneurysm of atherosclerosis.

Figure 3.—An intra-arterial digital subtraction aortogram shows a lobulated, 5-cm long contrast collection anterior to the distal abdominal aorta representing the saccular aneurysm with occlusion of the right common iliac artery.

An emergency operation showed an infected abdominal aortic aneurysm below the renal arteries that was ligated and resected. A left axillofemoral bypass and femoral-femoral crossover bypass graft from left to right was carried out to establish peripheral circulation to the lower limbs. The patient made an unremarkable recovery with sustained defervescence beginning one day postoperatively, and he was eventually discharged home with no sequelae.

Because of the risk of recurrent infection at the site of the resected aorta or of seeding of the prosthetic bypass graft, the patient was discharged on a regimen of oral cephalexin, which was to be continued indefinitely.

Discussion

The exact prevalence of aortic mycotic aneurysms is not known. In the preantibiotic era, most were due to infective endocarditis. The risk factors in the postantibiotic era, however, are arterial trauma (29%), depressed immunocompetence (24%), concurrent sepsis (17%), bacterial endocarditis (17%), congenital cardiovascular defects (10%), and primary aortic aneurysm (3%).[2] There is a male preponderance in a ratio of 3:1.[3] The pathogenesis is thought to be due to either septic aortic emboli from infective endocarditis, direct

or lymphatic extension from an adjacent infectious process, or hematogenous spread.[4] The emboli lodge in the vasa vasorum and produce a local arteritis, eventually resulting in necrosis and aneurysm formation.[5] The latest classification of mycotic aneurysms by Patel and Johnson dividing them with regard to the preexisting status of the artery and the source of infection is useful.[5]

In the preantibiotic era, *Streptococcus pyogenes* and *S pneumoniae* were prevalent, whereas in the postantibiotic era, viridans streptococci (30% to 40%), *Staphylococcus aureus* (10% to 25%), enterococci (5% to 15%), gram-negative bacilli (2% to 12%), and *Staphylococcus epidermidis* (1% to 3%) are common infecting organisms. Between 5% and 20% of cases are culture-negative. Cases due to *Salmonella* species have a tendency towards early rupture.[4] Although variable, the clinical presentation[2,6-8] includes fever (75%), back and abdominal pain (33%), abdominal pain and fever (20%), and palpable aneurysm (53%). In most cases, the onset is insidious, and low-grade fever may be present for several months. Because of the nonspecific symptoms and poor awareness of the condition among physicians, 75% rupture preoperatively. Rupture may occur into the peritoneal cavity, pleural cavity, duodenum, esophagus, mediastinum, or the pericardium. Laboratory findings include leukocytosis (65%), positive blood cultures (70%), aortic calcification (47%), and vertebral erosion (18%). Bacteremia is usually continuous and does not resolve with antibiotic treatment alone.

Mycotic aortic aneurysms have been described as "inevitably fatal,"[2] but early diagnosis followed by administering the appropriate antibiotics and timely surgical repair can result in cures of this otherwise lethal condition.[2,9] All patients without surgical treatment die of catastrophic hemorrhage or sepsis. The surgical treatment is aneurysmal resection with aortic interposition grafts or extra-anatomic bypass grafting. The antibiotic therapy should be continued for at least six to eight weeks.

The radiographic features of mycotic aneurysms previously described are erosion of lumbar vertebrae[6,10,11]; abnormal gas collections[8,12]; a soft tissue mass[10,11]; an absence of calcification indicating a nonatherosclerotic origin of an aneurysm[6]; an adjacent abscess[10]; an atypical site of involvement of the aorta, such as thoracoabdominal[11]; and a lobulated cystic structure on an ultrasonogram.[13] The angiographic findings described are those of an eccentric saccular aneurysm arising from one wall of the vessel without other associated atherosclerotic disease.[12,13] The clinical rapidity of the development of an aneurysm and signs of an infection and predisposing conditions are necessary for the diagnosis.[12]

Scintigraphy using leukocytes labeled with indium 111 has been reported useful in one case of a clinically occult mycotic aneurysm of the thoracic aorta with subsequent computed tomography used to distinguish between an abscess and an aneurysm.[7] Ultrasonography has been previously reported to show an abdominal aortic aneurysm with a subsequent diagnosis by computed tomography.[10] These previous reports showed either gas collections within the aneurysm wall or an adjacent abscess with destruction of an adjacent vertebral body. One case report indicates a large retroperitoneal mass encasing the abdominal aorta found on CT that initially had been thought to be lymphoma but was actually a paravertebral abscess.[10] The CT scan in our case shows a ring of calcification that must represent the intima of the aorta. This has surrounding soft tissue that at the time was not clearly appreciated to be the lumen of an aneurysm. An ultrasonogram shows that this does represent the lumen of the aortic aneurysm. This is further confirmed by a digital subtraction angiogram. No gas in the soft tissue structures was seen, nor was there any bone destruction or adjacent abscess.

On histopathologic examination of the resected aneurysm in our case, there were atherosclerotic changes with foci of suppuration in the wall. Unfortunately, no organism could be cultured, probably owing to antibiotic therapy. We postulate that prosthetic valve endocarditis developed that was partially treated. Subsequently, a preexisting atherosclerotic aortic aneurysm became infected hematogenously. This initially produced vague abdominal pains and persistent fever but was diagnosed at angiography. A high degree of suspicion by a clinician leading to early angiography and subsequent surgical treatment can prevent a lethal end to this difficult diagnostic problem.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Preventing Osteoporosis

To THE EDITOR: Dr Bruce Ettinger's article, "A Practical Guide to Preventing Osteoporosis," in the December 1988 issue,[1] brings out a number of interesting factors related to osteoporosis, but it also omits several.

I liked the analogy of the "bone bank account." Most "deposits" are made in adolescence and most "withdrawals" are made in the several years after menopause. It is my understanding that bone physiology is a dynamic process that continues throughout life, with a constant laying down of new bone and absorption of old bone. It would seem that absorption outstrips deposition in the later years of life. It is important that the bone bank deposit accounts be emphasized in the earlier years of life when one is in the building process.

Of the many different factors that influence calcium loss, Dr Ettinger makes no mention of some that may be of vital importance: high protein intake, caffeine, and carbonated beverages. He did mention that smoking reduces estrogen levels and that alcohol not only has a direct toxic effect on bone but is often associated with poor dietary habits, as well as decreased calcium absorption from the gut. Numerous studies have shown that high protein intake favors calcium loss in the urine. It is well documented that animal proteins are much more effective in promoting calcium loss in the urine than are proteins of vegetable origin. This appears to be because of the increased number of amino acids in animal proteins containing sulphur. The sulphur, apparently in its metabolic activity, changes the pH of the urine, favoring calcium loss. In addition, others have shown that high intake of caffeine increases urinary calcium loss. If we read the label on most carbonated beverages, we notice that one of the ingredients is phosphoric acid. High phosphate intake also is known to increase urinary calcium loss. Meat also has a high phosphorus content, and this may be one of the other factors, in addition to the high protein content, that favors excessive calcium loss in those with high meat intake. Some studies have shown that even men with very high protein intake cannot take enough calcium to put them in positive calcium balance.

It is quite well documented that most Americans ingest far more protein than they need. Protein intake in this country is particularly high in both meat and dairy products. It would seem to me that a practical program for the prevention of osteoporosis should begin in childhood by encouraging children to eat a diet that is adequate in protein, to minimize the intake of caffeinated and carbonated beverages, and to promote healthy exercise to stress the bones, which will encourage good mineral deposition. The diets that are advocated by both the American Cancer Society and the American Heart Association would have adequate protein and be low in total fat, particularly saturated fat and cholesterol, and high in fiber and vitamin and mineral content. The adoption of the life-style and eating habits promoted by the American Cancer Society and the American Heart Association would not only reduce the risk for cancer and cardiovascular disease but also for osteoporosis, diabetes, gallbladder disease, obesity, diverticulosis, diverticulitis, and a whole host of other disease entities.

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Public Health Notes

To THE EDITOR: Here are two public health concerns that we wish to bring to the attention of your readers.

Radon Testing of California Homes

In September 1988, the US Environmental Protection Agency (EPA) recommended that all homes in the nation be tested for the presence of radon. This recommendation was based on the recognized potential of radon to cause lung cancer and limited data from a survey of homes in 17 states showing elevated levels of radon in a significant number of homes in some of the states. California was not among the test states. Since the EPA's announcement, public interest in radon testing has increased notably, and we have received numerous queries from physicians requesting information on how they should advise patients.

Neither the California Department of Health Services (CDHS) nor the California Conference of Directors of Environmental Health currently recommend, as a matter of public policy, that all California homes be tested for radon. The generally mild climate, presence of predominantly low uranium content soils, and prevailing methods of home construction all militate against radon being a substantial problem in California. Likewise, specific sampling data from various parts of the state have found very few homes with elevated levels of radon. Indeed, to date, the study showing the greatest number of homes with elevated levels of radon was a survey conducted by the *Los Angeles Times,* with technical assistance from the CDHS and others, of 436 homes in Los Angeles, Riverside, Orange, San Bernardino, and Ventura counties that found 1.2% of test homes to have indoor air radon concentrations in excess of the EPA's action level of 4 pCi per liter. The overwhelming majority of homes having elevated radon levels were only mildly above the action level.

While the CDHS is currently conducting both statewide and geographically targeted testing of homes for radon contamination, we do not think that there is any reason for across-the-board testing. We do not discourage persons from having their homes tested for radon, however. If this is done,

though, we recommend an alpha track monitor be used instead of the charcoal canister device. We also encourage both medical practitioners and the public to learn more about this environmental agent and, toward that end, have produced a guidebook on radon. This book may be obtained by calling the CDHS Indoor Air Quality Program at (415) 540-2134.

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"Miraculous Insecticide Chalk"—An Unregistered Household Insecticide

The California Department of Health Services recently has received numerous reports of the sale of an unregistered insecticide for use against cockroaches and ants. This insecticide is prepared as a white stick simulating common blackboard chalk, and lines are drawn where the insects are to be controlled. It is manufactured in China and is not registered with either the US Environmental Protection Agency or the California Department of Food and Agriculture. This product is being sold to the public primarily through flea markets and Chinese import stores, with its use most often being reported in Asian restaurants and migrant labor camps.

Samples of "Miraculous Insecticide Chalk" submitted by the public have been found to contain 0.71% of a synthetic pyrethroid compound called deltamethrin. Deltamethrin is mildly toxic, with the most likely toxic manifestations being irritation of the mouth if ingested by a child. Ingesting small amounts—one piece of chalk or less—should require no medical therapy. Ingesting larger amounts should be managed supportively; no antidote is known. Since the product has not gone through the proper regulatory channels, we have no assurance that either active or inert ingredients pose only a minimal health hazard.

The sale of "Miraculous Insecticide Chalk" is illegal in California, and its use in restaurants is a violation of California's Health and Safety Code. Use of the product should be reported to local public health officials or local county agricultural commissioners.

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Screening for Sleep Apnea

To the Editor: The prevalence of sleep apnea is thought to be about 1% to 3%,[1] yet the medical literature infrequently reports efficient screening methods for this condition.[2] Screening is essential for cost containment.

We analyzed 33 polysomnography reports to determine a suitable method of screening patients before submitting them to full testing. We used the apnea-hypopnea index and a severity index to rate sleep apnea on a scale of zero to five. We found that an oximeter cutoff of 85% oxygen saturation would separate patients with 93% sensitivity and 75% specificity into a normal or mildly abnormal group versus those with clinically significant apnea.

We then used an oximeter[3] to screen 100 consecutive patients in their homes. Of those tested, 16 were normal (all O_2 saturations $\geq 90\%$) and a further 16 were mildly abnormal (lowest O_2 saturations, 85% to 89%). Desaturation episodes, when present, were seen clearly on the oximetry recorder strips, often in a "sawtooth" pattern suggesting obstruction.

We used a finger probe and a commercially available oximeter with stripchart (Biox IVA, Ohmeda Inc, Boulder, Colo). Patients had no difficulty with the device. We use the same device to evaluate the effect of follow-up continuous positive airway pressure[4] on the apnea.

We think patients can be safely and efficiently screened using portable oximetry. Our cost for polysomnography is $450 to $1,500, while oximetry costs $70—that is, about as much as an electrocardiogram.

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Amoxicillin Overdose With Gross Hematuria

To the Editor: Amoxicillin, even in cases of significant overdose, has proved to be remarkably safe. We report the case of a child, weighing 15 kg (33 lb), who took between 5 and 11 grams of the suspension and, without any allergic signs or indications of compromised renal function, had gross hematuria, which cleared without sequelae.

Report of a Case

The patient, a 3-year-old boy, had been treated for one day with amoxicillin for an upper respiratory tract infection. Three hours before admission to hospital, he ingested between 5 and 11 grams of the suspension, taking both his own and his brother's medication. He was managed initially with outpatient observation. Shortly before admission, he complained that his penis hurt. He was then seen in the emergency department.

The patient's history was remarkable in that he was the product of a 43-week gestation and had Apgar scores of 2 and 8. He received antibiotics for 48 hours after birth and went home on the fifth postpartum day. With the exception of several bouts of otitis media, he had been well and had received routine care and immunizations.

On physical examination the patient was in no distress. He was afebrile; his blood pressure was 90/50 mm of mercury, respirations were 24, and he had a pulse rate of 96. The results of a general physical examination were unremarkable. He had one episode of emesis in the emergency department. A urinalysis showed packed red blood cells, with macroscopic crystals seen. There were no casts or other abnormalities. The patient's hemoglobin level was 124 grams per liter, blood urea nitrogen 5.7 mmol per liter (16 mg per dl), and creatinine 61.9 μmol per liter (0.7 mg per dl).

He was admitted to hospital and hydrated. A chemical screen was negative. His clotting variables were all within normal limits, the leukocyte count was 9.4×10^9 per liter without eosinophilia, and his hemoglobin level was stable. A urine culture was negative. Within 24 hours, the urine cleared, showing only 0 to 1 red blood cell per high power field. An intravenous pyelogram showed bilateral partial midureteral obstructions, possibly on a congenital basis. The child has been well since discharge; a follow-up intravenous pyelogram is planned in six months.

In a previous case in the literature,[1] gross hematuria was recorded after a 3-year-old child ingested 7 grams of amoxicillin for a total dose of 574 mg per kg. This child exhibited lethargy and vomiting within three hours, progressing to oliguria and a deterioration in renal function, with the creatinine level increasing to 318.2 μmol per liter (3.6 mg per dl). There were no allergic manifestations, and the child's condition improved with intravenous hydration, regaining normal renal function within 72 hours.

Appel and co-workers[2] described a patient in whom acute interstitial nephritis developed while she was receiving intravenous amoxicillin. She also had a rash, eosinophilia, fever, and nonoliguric renal failure. Tannenberg and colleagues reported an instance of nonazotemic nephropathy associated with ampicillin therapy.[3] A 12-year-old boy was given 500 mg intramuscularly, followed by 500 mg orally, and nausea, emesis, and fever then developed. His urine showed many red blood cells; creatinine and blood urea nitrogen levels were normal. A renal biopsy three weeks later showed an irregular interstitial reaction with infiltration of mononuclear cells, primarily lymphocytes, and a few eosinophils. Maxwell and associates describe a similar syndrome with rash, followed by edema and increasing creatinine levels, during intravenous ampicillin therapy.[4] They thought that their patient had accumulated massive amounts of ampicillin in her system, leading to the renal insufficiency. As the antibiotic levels fell, her renal function improved.

Our case is probably that of a drug-induced hemorrhagic cystitis, with the patient presenting with gross hematuria and the absence of casts, increased creatinine, or other features suggesting a renal origin. Cases of hemorrhagic cystitis due to ticarcillin[5] and carbenicillin[6] therapy have been reported. Ours is the first report of this syndrome due to amoxicillin therapy.

This child's cystitis cleared rapidly when the drug therapy was stopped and the child hydrated. No sequelae were apparent. Cross sensitivity among penicillins may require that the patient avoid this therapy in the future.

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Medical Student Writing Award Runner-up

Tuberculosis in Patients With Human Immunodeficiency Virus Infection

Review of Current Concepts

CHARLES P. THEUER, MD, *San Francisco*

Tuberculosis is a frequent complication of human immunodeficiency virus (HIV)-induced immunosuppression. The diagnosis of extrapulmonary tuberculosis in patients with evidence of HIV infection qualifies as a criterion of the acquired immunodeficiency syndrome. Demographic characteristics of patients with tuberculosis and HIV infection vary by region and reflect the degree to which patients with Mycobacterium tuberculosis *infection adopt behaviors that put them at risk for HIV infection. The clinical features of tuberculosis in patients with HIV infection are atypical. Extrapulmonary disease, tuberculin anergy, and unusual findings on chest radiographs occur most frequently when tuberculosis afflicts patients with other clinical evidence of HIV infection at the time tuberculosis is diagnosed. Treatment is effective for tuberculosis in HIV-seropositive patients, and isoniazid prophylaxis is recommended for HIV-infected patients with positive tuberculin skin tests.*

(Theuer CP: Tuberculosis in patients with human immunodeficiency virus infection—Review of current concepts. West J Med 1989 Jun; 150:700-704)

Tuberculosis, once a leading cause of infectious mortality, is now considered an uncommon disease. What may surprise physicians, however, is that tuberculosis morbidity is on the rise in the United States. This increase has occurred at a time of an increasing prevalence of human immunodeficiency virus (HIV) infection.

Mycobacterium tuberculosis, the causative agent of tuberculosis, is an obligate aerobe that classically produces disease in patients with depressed cell-mediated immunity. Diabetes mellitus, ethanol abuse, and steroid dependence have each been associated with an increased risk of tuberculosis, presumably through this mechanism. The human immunodeficiency virus, the causative agent of the acquired immunodeficiency syndrome (AIDS), preferentially infects helper T lymphocytes and leads to profound deficits in cell-mediated immunity.[1] As expected, studies have shown an increased prevalence of tuberculosis in patients with HIV infection.

These studies have also shown that the clinical features of tuberculosis in patients with HIV infection differ from those of tuberculosis occurring in HIV-seronegative patients. In addition, they have shown that tuberculosis is curable regardless of a patient's HIV status.

The purpose of this review is to inform primary care physicians of the unique epidemiologic and clinical features—as well as the proper treatment—of tuberculosis occurring in HIV-infected patients. By recognizing the unique features of HIV-associated tuberculosis, treatment can be initiated early and further morbidity avoided.

Epidemiology

In 1986 the Centers for Disease Control reported a smaller decrease in reported tuberculosis cases in 1985 as compared with the two previous years.[2] The following year the number of tuberculosis cases exceeded the 1985 number.[3] This marked the first substantial annual increase in tuberculosis cases in 30 years. Several lines of evidence suggest that HIV infection accounted in part for the increased tuberculosis morbidity observed over this period.

Ecologic studies were the first to suggest a tuberculosis-AIDS association: New York City health districts reporting the highest incidence of AIDS also reported the highest incidence of tuberculosis.[4] Subsequent retrospective studies matching AIDS and tuberculosis patients in New York, Newark (New Jersey), Miami, and San Francisco revealed a prevalence of tuberculosis in AIDS patients ranging from 2% in San Francisco to 34% in Miami.[5-11] These figures exceeded the estimated national tuberculosis incidence and reinforced a link between HIV and tuberculosis.

Population-based retrospective studies in New York, Miami, and San Francisco showed that, when compared with patients with tuberculosis without AIDS, patients with tuber-

From the University of California, San Francisco, School of Medicine. This paper was the runner-up in *The Western Journal of Medicine's* 1989 Medical Student Writing Award Competition. At the time of the contest, Dr Theuer was a fourth-year medical student; he obtained his MD degree in May 1989.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
IV = intravenous
PPD = purified protein derivative
TB = tuberculosis

culosis (TB) and AIDS—henceforth referred to as TB-AIDS patients—tended to be younger (usually in their mid-30s) and more often men.[5,10,11]

Racial and ethnic characteristics of TB-AIDS patients defined retrospectively were dependent on study location and design. Of patients admitted to a Newark hospital, 76% were non-Haitian black compared with 17% in San Francisco.[6,11] Most TB-AIDS patients in Miami were Haitian (96%), but none in San Francisco were Haitian.[5,11] The proportion of Latino TB-AIDS patients varied from 38% in a New York hospital to 7% in a Newark hospital.[6,7] Foreign-born TB-AIDS patients predominated in Miami but were less frequently seen at other locations.[5]

The presence of intravenous (IV) drug use as an HIV transmission factor ranged from 83% of TB-AIDS cases in Newark to 17% in San Francisco.[6,11] Even in San Francisco, however, where 80% of TB-AIDS cases occurred in homosexuals, IV drug use was more commonly associated with TB-AIDS cases than with cases of AIDS not complicated by tuberculosis.[11]

It became clear that the demographic features of TB-AIDS patients reflected the degree to which populations with *M tuberculosis* infection adopted behaviors that put them at risk for HIV infection—that is, high-risk sexual intercourse, IV drug use, or blood product exposure. In San Francisco, for instance, blacks—who represent one of every three cases of tuberculosis—accounted for few AIDS cases.[11] When compared with patients with AIDS but not tuberculosis, then, TB-AIDS patients were more likely to be black than white. In comparison to patients with tuberculosis but not AIDS, however, TB-AIDS patients were more likely to be white. In Miami, where *M tuberculosis* infection is endemic among Haitians and AIDS also develops in many, it is no surprise that Haitians represented almost all cases of tuberculosis and AIDS.[5]

Retrospective studies defined the prevalence and demographic features of tuberculosis in AIDS patients but did not address the question of tuberculosis occurring in HIV-infected patients not yet immunocompromised sufficiently to manifest AIDS. Prospective studies, by defining the seroprevalence of HIV infection in tuberculosis patients, overcame this limitation because they were able to identify cases of HIV-seropositive patients in whom tuberculosis developed but who otherwise had no evidence of HIV infection.

Prospective seroprevalence studies in Miami and San Francisco showed that 31% and 28%, respectively, of patients with tuberculosis were also infected with HIV.[12,13] These prevalence figures were higher than AIDS prevalence figures in cases of tuberculosis identified retrospectively (for instance, 12% of tuberculosis patients from 1981 to 1985 in San Francisco had AIDS) and indicated that most tuberculosis cases occurred in asymptomatic HIV-infected patients.

Prospective evaluation also pointed out that the demographics of HIV-related tuberculosis had changed. In San Francisco, where IV drug use accounted for only 17% of TB-AIDS cases during a retrospective study period from 1981 to 1985, about half of HIV-seropositive tuberculosis patients were intravenous drug users during the prospective period from 1986 to 1988.[11,13] The emergence of IV drug use as the major HIV transmission factor in HIV-seropositive patients with tuberculosis is not surprising.

Public health efforts have substantially reduced homosexual HIV transmission, but transmission by IV drug use remains a major public health problem.[14] The fact that intravenous drug users are at an increased risk of *M tuberculosis* infection independent of their HIV status further compounds the problem.[15,16] In the future, it is likely that the proportion of IV drug users with HIV infection contributing to tuberculosis morbidity will increase unless effective means for controlling HIV transmission in this group are found. As a result, racial minorities, who are overrepresented among intravenous drug users, can be expected to make up a greater proportion of HIV-related tuberculosis cases.[17]

Clinical Features

Tuberculosis is the initial opportunistic infection in many HIV-seropositive patients—presumably because of the highly virulent nature of *M tuberculosis* infection as compared with other opportunistic infections associated with HIV disease. Of 15 of 17 HIV-seropositive patients in San Francisco, 1 had a previous episode of Kaposi's sarcoma and 1 had oral candidiasis before the diagnosis of tuberculosis.[13] The rest did not have clinical evidence of HIV infection apart from tuberculosis. Similarly, of 22 HIV-seropositive patients with tuberculosis in Miami, only 2 met Centers for Disease Control criteria for AIDS before the diagnosis of tuberculosis—both had *Pneumocystis carinii* pneumonia—and 4 were classified as having AIDS-related complex by virtue of oral candidiasis, persistent diarrhea, or unexplained generalized lymphadenopathy.[12]

As expected, the lung was the most commonly involved site in tuberculosis patients with HIV infection, as pulmonary tuberculosis occurred in 74% to 79% of cases.[5-13] Patients with tuberculosis and AIDS also showed high rates of extrapulmonary disease, ranging from 45% to 72%.[5-11] These figures were much higher than the national average of 16%.[18] A similar rate of extrapulmonary disease in HIV-seropositive patients with tuberculosis but not AIDS was found in Miami, though a prospective study in San Francisco showed that asymptomatic HIV-seropositive patients with tuberculosis do not have higher rates of extrapulmonary disease when compared with HIV-seronegative controls.[12,13]

The San Francisco data show that the clinical features of tuberculosis in HIV-infected patients reflect the stage of HIV infection. Patients with AIDS are more severely immunocompromised than HIV-infected patients without clinical evidence of infection and can therefore be expected to have higher rates of disseminated tuberculosis and other atypical clinical features.

The most frequent sites of extrapulmonary tuberculosis in HIV-infected patients were the lymphatic, genitourinary, and hematologic systems.[5,6,8,11] Other commonly noted sites were the central nervous and musculoskeletal systems.[11] Occasionally multiple extrapulmonary sites of disease were identified in a single patient. For unclear reasons, tuberculosis in patients with AIDS seemed not to disseminate frequently to the pleura.[5,6,11] Reports did not specify pleural fluid sampling rates, however, and pleural effusions, while of

less volume, occurred as commonly as in patients with tuberculosis not complicated by AIDS.[11,19]

The chest radiograph is atypical in TB-AIDS patients with pulmonary disease. Frequently the radiographic pattern resembled that of primary tuberculosis, with middle or lower lobe infiltration.[19] Classic apical disease was rarely found.[7,11,19] Patients with TB and AIDS also manifested intrathoracic (hilar or mediastinal) lymphadenopathy in 20% to 59% of patients in comparison with 0% to 3% in patients with tuberculosis without AIDS.[6,11,19] Diffuse infiltration was more common (18% to 60%), although occasionally concurrent pulmonary infections caused this radiographic finding.[11,19] Cavitation was less common than in cases of tuberculosis without AIDS though it was observed 0% to 23% of the time.[6,7,11,19]

In patients with tuberculosis and HIV infection but not AIDS, the radiographic appearance is more typical. Cavitation was seen in 31% of HIV-seropositive patients with pulmonary tuberculosis in San Francisco (and occurred only slightly less frequently than the 34% seen in HIV-seronegative patients with pulmonary tuberculosis).[13] The absence, however, of cavitation and other atypical features remained significantly more common in HIV-seropositive patients—most of whom did not have AIDS—with pulmonary tuberculosis in south Florida.[12]

The acid-fast smear remains a very useful tool in HIV-seropositive patients with tuberculosis. In cases of pulmonary tuberculosis, patients with HIV infection had acid-fast bacilli on a smear in 47% to 67% of cases, as compared with 40% to 51% in HIV-seronegative patients.[12,13]

Approximately 85% of HIV-seronegative patients with tuberculosis have a positive (greater or equal to 10 mm of induration) tuberculin skin test.[18] In contrast, TB-AIDS patients had rates of tuberculin anergy ranging from 60% to 93%, making the tuberculin test unreliable in these patients.[5-7,11] Anergy in cases of HIV infection (but not necessarily AIDS) identified prospectively ranged from 50% in Miami to only 20% in San Francisco, indicating that tuberculin testing can be a useful screening test in asymptomatic HIV-infected patients with *M tuberculosis* infection.[12,13]

Diagnosis

It is important to diagnose tuberculosis in cases of HIV infection and also to diagnose HIV infection in patients with tuberculosis. Tuberculosis in HIV-seropositive patients is curable.[20] From a social standpoint, patients with extrapulmonary tuberculosis and HIV infection are considered to have AIDS and qualify for certain social support benefits.

The workup of an HIV-infected patient thought to have tuberculosis should be expeditious to facilitate early therapy. Every HIV-infected patient should be questioned as to a history of tuberculosis, tuberculosis exposure, or tuberculin reactivity. Other aspects of the history that are useful, albeit nonspecific, include the presence of cough, dyspnea, fever, chills, night sweats, fatigue, or weight loss. Symptoms will typically have been present for a number of weeks, though many other HIV-related diseases also present with a subacute course.

Most HIV-seropositive patients with tuberculosis have pulmonary disease, so the initial laboratory evaluation should begin with a chest radiograph. Classic apical disease is rare in HIV-seropositive patients, and pulmonary tuberculosis in AIDS patients may present with any of a number of radiographic patterns, ranging from lobar infiltrates to diffuse reticular patterns. The atypical radiographic appearance makes it hard to "rule in" or "rule out" tuberculosis based solely on the radiograph.

Frequently the radiographic pattern is indistinguishable from that caused by other HIV-related pulmonary opportunists—especially *P carinii*, the most common pulmonary pathogen in AIDS patients. In this regard, intrathoracic lymphadenopathy—a feature rarely seen in *P carinii* pneumonia—is commonly seen in AIDS patients with tuberculosis. The presence of this feature makes the diagnosis of tuberculosis more likely, although other conditions, most notably pulmonary Kaposi's sarcoma, also present with this finding.

The poor specificity of the chest radiograph in cases of HIV-associated tuberculosis makes sputum analysis for acid-fast bacilli an essential diagnostic tool. At least three sputum specimens obtained for acid-fast bacilli should be the rule rather than the exception in HIV-infected patients with pulmonary disease. The inadequacy of the chest radiograph as a diagnostic tool is perhaps best shown by the fact that *M tuberculosis* has been grown from sputum cultures of AIDS patients whose only sign was intrathoracic lymphadenopathy on a chest x-ray film.[19]

Various extrapulmonary sites are commonly affected in HIV-infected patients with tuberculosis. Clinicians should get a specimen from all suspicious sites and send it for acid-fast stain and culture. As well, when indicated clinically, culturing of blood, urine, and stool specimens—in addition to sputum—for acid-fast organisms should be done.

While diagnosing tuberculosis in HIV-infected patients is essential, it is also important to document HIV infection in patients with tuberculosis. The identification of this combination of disease is paramount to HIV education efforts and to define the appropriate duration of antituberculosis chemotherapy. Furthermore, those patients with extrapulmonary tuberculosis and evidence of HIV infection will be classified as having AIDS.

The documenting of HIV infection can be accomplished with HIV antibody testing. The presence of HIV transmission factors may be a useful guide in selecting cases for antibody testing, although 24% of HIV-seropositive patients with tuberculosis in San Francisco did not report HIV risk factors on careful questioning.[13] Hence, in areas with a high degree of concomitant HIV and *M tuberculosis* infection, HIV antibody testing of all cases of tuberculosis has been advocated.[20]

Therapy and Prognosis

Tuberculosis is one of the most treatable complications of HIV infection; it is also one of the few that are contagious. As a result, antituberculous chemotherapy should be started whenever acid-fast bacilli are found from a tissue site in patients with proven or suspected HIV infection. If subsequent culture results show that acid-fast bacilli are *Mycobacterium avium-intracellulare* complex, the therapy can be altered.

Prospective and retrospective studies showed excellent clinical and microbiologic responses of tuberculosis in HIV-infected patients complying with four-drug chemotherapy. In pulmonary cases, sputum conversion occurred as quickly as in HIV-seronegative patients, generally within three months of initiating treatment.[5-7,11-13]

Radiographic abnormalities similarly abated, and extrapulmonary foci, while usually not subjected to biopsy to document a microbiologic cure, became clinically inapparent.[5-7,11-13] In this regard, however, in two patients with TB and AIDS in Newark with central nervous system tuberculosis and one patient with pericardial tuberculosis, disease progressed despite appropriate chemotherapy.[6] More importantly, one patient successfully treated in Newark for pulmonary tuberculosis relapsed at an extrapulmonary site despite an apparent compliance with four-drug therapy.[21]

Based in part on these treatment failures and the theoretic concern that inadequate host defenses may allow microorganisms to persist, current Centers for Disease Control recommendations for the treatment of tuberculosis in HIV-seropositive patients are different from those applicable to patients without evidence of HIV infection.

Treatment should be started with isoniazid (INH), 300 mg per day; rifampin, 600 mg per day (or 450 mg for patients weighing less than 50 kg); plus pyrazinamide, 20 to 30 mg per kg body weight per day, during the first two months of therapy. Ethambutol hydrochloride, 25 mg per kg per day, should be included if central nervous system or disseminated disease is present or when isoniazid resistance is suspected.[20]

In contrast to the six-month short-course therapeutic regimen recommended for HIV-seronegative patients with tuberculosis, the treatment of HIV-seropositive patients should continue for nine months and for at least six months after documented culture conversion. If either isoniazid or rifampin—both bactericidal antimicrobials—is not, or cannot be, included in the treatment regimen, therapy should continue for a minimum of 18 months and for at least 12 months after culture conversion.[20]

It should be noted, however, that standard four-drug short-course therapy continues to be used in San Francisco for uncomplicated (purely pulmonary) HIV-related tuberculosis with excellent results (G. F. Schecter, MD, oral communication, May 1989).

Adverse reactions to antituberculous medications necessitating a change in therapy occurred in a substantial number (26%) of TB-AIDS patients in San Francisco, compared with the 3% figure reported for patients with tuberculosis without AIDS. Rash and itching due to isoniazid or rifampin accounted for most toxic reactions, and one patient each had isoniazid hepatitis and rifampin-induced thrombocytopenia.[11] In south Florida, liver function test elevations were common in TB-AIDS patients, though only 8% required discontinuing rifampin therapy because of significant hepatitis.[5]

Prospective studies focusing mainly on HIV-seropositive patients with tuberculosis but no other clinical evidence of HIV infection did not show increased rates of drug toxicity in patients with HIV infection.[12,13] In no case, identified retrospectively or prospectively, has therapy failed because antituberculous medication therapy was discontinued due to an adverse drug reaction.[5-7,11-13]

Contacts of the index case must be traced in all cases of tuberculosis regardless of a patient's HIV status. Data from south Florida showed that 35% of close contacts of HIV-seropositive patients with tuberculosis had tuberculin reactivity.[12] In comparison, 44% of close contacts of HIV-seronegative patients with tuberculosis showed tuberculin reactivity.[12] This difference was not statistically significant, and there is no evidence that HIV-seropositive patients with tuberculosis are less or more infectious than their seronegative counterparts.

The survival of TB-AIDS patients is poor. Patients in San Francisco lived an average of 7.4 months after the diagnosis of tuberculosis and 8.1 months after the diagnosis of AIDS.[11] Death was related to HIV complications other than tuberculosis. Prospective studies indicate a longer life span for HIV-infected patients with tuberculosis without other clinical evidence of HIV infection.[12,13] Because of limited follow-up, the exact prognosis of these patients is unknown. Within the next few years, survival estimates should become available.

Prevention

Preventive therapy is advocated for all HIV-seropositive patients with evidence of *M tuberculosis* infection.[20] The tuberculin skin test is relatively sensitive for proving *M tuberculosis* infection in asymptomatic HIV-infected patients without AIDS and—because it is inexpensive—clinicians should routinely do tuberculin testing on HIV-seropositive patients.

Unfortunately, there is no other widely available test for proving *M tuberculosis* infection. Recent work has shown that antibodies to purified protein derivative (PPD) are present in some anergic HIV-seropositive patients with tuberculosis. If PPD antibody testing becomes widely available, it may become a useful adjunct for proving *M tuberculosis* infection in an anergic HIV-seropositive patient.[22]

Patients with documented *M tuberculosis* infection should be treated with isoniazid, 300 mg per day, for 12 months. Because the efficacy of this regimen is unproved, patients should be observed closely at the completion of therapy for the development of tuberculosis.[20]

Summary

Tuberculosis is a significant HIV-related disease. Since 1987 extrapulmonary tuberculosis in a patient with evidence of HIV infection has qualified as a diagnosis of AIDS. The demographic characteristics of patients with HIV infection and tuberculosis reflect specific locales. Recent evidence indicates that IV drug use has emerged as the predominant HIV transmission factor in these patients. The clinical features of tuberculosis in patients with HIV infection are atypical. Extrapulmonary disease, tuberculin anergy, and infrequent apical disease on chest radiograph occur most frequently when tuberculosis afflicts patients with other clinical evidence of HIV infection at the time tuberculosis is diagnosed.

Tuberculosis is a curable disease regardless of a patient's HIV serologic status, although HIV-seropositive patients should receive a longer course of chemotherapy. Isoniazid prophylaxis is advocated in all HIV-seropositive patients with *M tuberculosis* infection—that is, those with positive tuberculin skin tests. The prognosis for HIV-infected patients treated for tuberculosis is poor but reflects the underlying immunosuppression induced by HIV infection rather than complications stemming from tuberculosis.

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Health Care Delivery

Understanding of Elderly Patients' Resuscitation Preferences by Physicians and Nurses

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We compared the understanding by family physicians and nurses of their elderly outpatients' preferences for cardiopulmonary resuscitation and mechanical ventilation under 3 scenarios reflecting varying qualities of life. Physicians and nurses correctly predicted patients' treatment preferences in from 59% to 84% and 53% to 78% of cases, respectively, for the various decisions. For most decisions, neither physicians nor nurses were significantly more accurate in their predictions than expected by chance alone. Moreover, nurses and physicians did not significantly agree with one another in their predictions of patients' preferences for any of these decisions. These results suggest that while nurses' and physicians' perceptions of patients' preferences for life-sustaining treatment are not necessarily similar, neither nurses nor physicians systematically understand their elderly patients' resuscitation preferences.

(Uhlmann RF, Pearlman RA, Cain KC: Understanding of elderly patients' resuscitation preferences by physicians and nurses. West J Med 1989 Jun; 150:705-707)

Making medical decisions for patients who become incapable of decision making is among the most challenging aspects of medical practice. As with other adult patients, decisions for such patients ideally should be based on their values, as well as their prognoses. By definition, however, the medical management "preferences" of such patients must be inferred. This process, which has been termed "substituted judgment," has been endorsed as the preferred method for surrogate decision making.[1]

Studies to date suggest that physicians generally lack the systematic understanding of their patients' resuscitation preferences necessary to make valid substituted judgments.[2-4] Nevertheless, such decisions are often made independently by physicians without the involvement of others who may be knowledgeable of, or provide care for, the patient.[5-7] Nurses, in particular, often have close physical and emotional ties to patients.[7] In addition, nurses, by virtue of their clinical responsibilities in implementing physicians' orders, should be involved in medical decisions, particularly those with "ethical" connotations.[8] Thus, the understanding of patients' preferences by nurses merits exploration. Previous studies have consistently shown that nurses and physicians differ in their personal preferences regarding various patient treatment decisions.[6,7,9,10] These studies, however, have not investigated the relative capacities of physicians and nurses for substituted judgment. We compared the ability of family physicians and nurses to predict life-sustaining treatment preferences of elderly, chronically ill patients, a population at risk for both acute and chronic mental incapacity.

Methods

Subjects

The study was done at Group Health Cooperative of Puget Sound, the largest health care cooperative and health maintenance organization in the state of Washington. Physicians were randomly selected from among all primary care physicians (all of whom were family practitioners) at the six permanently staffed Group Health Cooperative primary care outpatient clinics in Seattle. Physicians selected by this process were sent an approach letter and then telephoned by study personnel. Of 26 physicians approached, 19 (73%) agreed to participate. Nurses and physicians in the Group Health Cooperative's clinics are paired in teams so that the same nurse and physician follow each patient longitudinally. In addition, the primary care physicians retain primary responsibility for their clinic patients when they are admitted to hospital. All 19 nurses paired with participating physicians agreed to participate in this study.

The appointment logs of participating physicians were reviewed to identify the ten most recently seen patients fulfilling entry criteria. These criteria were age 65 years or older, the presence of at least one chronic disease, at least one visit to the index physician in the past six months and two visits in the past year, not demented, and not terminally ill. Patients were considered demented if they carried the diagnosis of dementia or had a legal guardian. Patients were deemed "terminally ill" if a physician estimated the patient's life expectancy to be less than six months.

Of 190 patients who fulfilled entry criteria, 69 (36%)

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responded to an approach letter. From among these, a maximum of four patients from each practice was randomly selected and asked to participate in the study. (In some practices, fewer than four patients returned postcards.) Of 55 patients asked to participate, 52 (94%) consented to do so.

Determining Resuscitation Preferences

Patients' preferences for cardiopulmonary resuscitation (CPR) and CPR plus a ventilator in the event of cardiac arrest—described as a "sudden heart stoppage"—were elicited with a reliable self-administered questionnaire.[4] For several patients who were visually impaired, the questionnaires were administered by an interview. Resuscitation preferences were scored on a five-point Likert scale with responses ranging from "definitely yes" to "definitely no." For the CPR-plus-ventilator decisions, the ventilator was described as being required for an "indefinite period of time" to "help you breathe" and "remain conscious." Physicians and nurses were instructed to predict patients' preferences and did so blinded to one another's and the patients' responses. Aside from contextual modifications, the questions were identical in all versions of the questionnaires.

To more fully characterize physicians' and nurses' potential surrogate decision-making abilities, we elicited preferences for CPR and CPR plus ventilator under three scenarios representing health states with varying prognoses and qualities of life.[3,11] In the "current health" scenario, cardiac arrest occurs with a patient in his or her "own current health and life situation." In the other scenarios, cardiac arrest occurs during a hospital stay for the treatment of one of two incapacitating illnesses, stroke and chronic lung disease, which were described as being superimposed on the patient's current health status. In the stroke scenario, the patient is described as being immobile, aphasic, and functionally dependent: "You are paralyzed so that you cannot walk and have difficulty speaking and feeding yourself. You would need constant attention and assistance for basically everything you do." In the chronic lung disease scenario, the patient has incapacitating, irreversible dyspnea: "You would not be able to climb stairs or walk more than a few feet; the condition would not be expected to improve."

Statistical Analysis

To make the analyses of agreement between patients, nurses, and physicians more reflective of the dichotomous nature of clinical decision making, the five-point resuscitation scales were collapsed into two categories, "yes" (consisting of "definitely yes," "probably yes," and "uncertain") and "no" (consisting of "probably no" and "definitely no"). An "uncertain" response was counted as a "yes" because, under conditions of uncertainty, the recommended presumption is to treat.[1] Responses were also analyzed in their original uncollapsed, five-point format to confirm that the dichotomous scale would not alter conclusions regarding the statistical significance.[4] Agreement was expressed in terms of proportionate (%) agreement. Because proportionate agreement is biased by the underlying distribution of responses, agreement independent of chance was also expressed with κ for agreement[12]—κ having a maximum value of 1, indicating perfect agreement. Values not statistically significantly greater than 0 imply no greater agreement than expected by chance alone. Statistical significance levels are two-tailed.

Results

The patients were elderly, predominantly women, and reported minor, if any, functional limitations (Table 1). They generally had received care from their physicians and nurses for several years or more and had made frequent clinic visits in the past year. On an average, physicians globally rated their patients' health as between "good" and "fair, not too good," and as "about . . . average" for others their age and sex.

Patients' treatment preferences varied considerably among the scenarios (Table 2). Nurses tended to overestimate patients' preferences in favor of resuscitation; none of these differences were statistically significant, however. Physicians appeared neither more likely to overresuscitate nor to underresuscitate in regard to patients' preferences. Agreement with patients ranged between 59% and 84% for physicians and 53% and 78% for nurses. (Thus, disagreement ranged from 16% to 41% for physicians and 22% to 47% for nurses). The κ values indicated that the predictions of patients' preferences were significantly more accurate than expected because of chance alone for only one decision each for physicians (chronic lung disease: CPR plus ventilator) and nurses (stroke: CPR plus ventilator). The κ values, however, were modest-sized.[13]

Neither physicians nor nurses accurately predicted patients' preferences, and we wondered whether this was due to a common bias among them. Consequently, we next compared agreement between physicians and nurses. For five of six decisions, nurses were more likely than physicians to think patients preferred resuscitation (Table 2). These differences were statistically significant for the chronic lung disease-CPR and stroke-CPR decisions. Agreement between physicians and nurses ranged from 48% to 80% across the scenarios (Table 3). As indicated by the κ values, however, in no instance was the level of agreement between physicians and nurses greater than that expected by chance alone.

TABLE 1.—*Patient Characteristics*

Patient Characteristics	*Patients, n=52*
Mean age, yr	74.0
Female, %	76.9
Married, %	48.1
Median duration of physician-patient relationship, yr	4.8
Median duration of nurse-patient relationship, yr	2.8
Admitted to hospital in past 12 mo, %	29.8
Median No. office visits with index physician in past 12 mo	5.5
Mean global health, physician-rated*	3.3
Mean relative health, physician-rated†	2.9
Mean functional impairment, patient-rated‡	2.7
Leading diagnoses, %	
Arthritis	32.7
Hypertension	23.1
Ischemic heart disease	17.3
Cancer	13.5
Depression	11.5
Chronic lung disease	7.6

*"With regard to your patient's health during the past year, would you rate it as: 1=perfect, couldn't be better; 2=very good; 3=good; 4=fair, not too good; or 5=not good at all?"

†"Compared with most persons your patient's age and sex, how would you rate your patient's health? 1=much better than most persons; 2=somewhat better than most persons; 3=about the same, average for most persons; 4=somewhat worse than most persons; 5=much worse than most persons."

‡"Do you have chronic illness or a medical or physical condition that limits your activity? 1=no, none; 2=yes, but virtually no limitations on my activity; 3=yes, but only a small limitation on my activity; 4=yes, with some real limitations on my activity; 5=yes, with serious limitations on my activity."

TABLE 2.—*Accuracy of Physicians' and Nurses' Predictions of Patients' Resuscitation Preferences*

Contingent Scenarios and Treatment	Prefer Resuscitation for the Patient, %			Agreement With Patients, %		Agreement With Patients, $\kappa \pm SD$*	
	Patients	MDs	RNs	MDs	RNs	MDs	RNs
Chronic lung disease							
CPR	73	67	84†	63	67	.12±.14	−.01±.13
CPR plus ventilator	24	33	35	71	67	.29±.14‡	.22±.14
Stroke							
CPR	29	24	45†	59	53	−.05±.14	.02±.13
CPR plus ventilator	14	16	24	75	78	−.02±.14	.30±.13‡
Current health							
CPR	86	94	86	84	77	.13±.13	.01±.14
CPR plus ventilator	28	37	41	67	65	.25±.14	.24±.14

CPR=cardiopulmonary resuscitation

*κ for agreement ± standard deviation (SD): 1=perfect agreement, 0=random agreement, <0=disagreement.
†$P<.05$ for physician-nurse difference by McNemar's test.
‡95% confidence interval for $\kappa>0$.

TABLE 3.—*Concordance of Nurses and Physicians in Predicting Patients' Resuscitation Preferences*

Contingent Scenarios and Treatment	MD-RN Agreement	
	%	$\kappa \pm SD$*
Chronic lung disease		
CPR	66	.13±.13
CPR plus ventilator	50	−.10±.14
Stroke		
CPR	60	.15±.13
CPR plus ventilator	60	−.24±.14
Current health		
CPR	80	−.09±.13
CPR plus ventilator	48	−.08±.14

CPR=cardiopulmonary resuscitation

*κ for agreement ± standard deviation (SD): 1=perfect agreement, 0=random agreement, <0=disagreement.

Discussion

Nurses, by virtue of their training and clinical responsibilities, are logical participants in decisions regarding life-sustaining treatment.[8] Moreover, nurses frequently think they can offer unique contributions to ethically problematic clinical decisions.[14] Such contributions are potentially valuable given the lack of evidence that physicians understand their patients' preferences for life-sustaining treatment.[2-4]

As in other populations,[2,3] physicians in this study did not show a systematic understanding of their patients' preferences for various life-sustaining treatments.[4] The results of this study, however, do not support the hypothesis that nurses understand patients' preferences for such treatment; nurses were not systematically accurate in predicting patients' preferences. Indeed, these results suggest that nurses may tend to be more aggressive in resuscitation than patients prefer. These differences were not statistically significant, however, and as such require confirmation in a larger sample.

These results do not provide evidence that physicians and nurses share a common bias in their perceptions of patients' preferences for life-sustaining treatment. For instance, for some decisions, nurses' and physicians' predictions of patients' preferences differed significantly. In addition, under none of the scenarios studied did κ values show large or statistically significant levels of agreement between nurses and physicians.

Physicians and nurses in this study predicted patients' preferences blind to one another's responses. Thus, the contribution of nurses to such decision making in actual clinical practice, in which an unblinded, negotiated process is more likely, may differ. It seems unlikely, however, that such a conjoint process would result in an enhanced understanding of patients' preferences if neither physicians nor nurses independently understand their patients' preferences.

Additional information is needed before general conclusions can be drawn regarding the relative accuracy of physicians' and nurses' substituted judgments. Notably, our sample was relatively small and, by virtue of its being derived from a single health maintenance organization, may be atypical. In addition, the representativeness within this setting of the modest proportion of patients who agreed to participate in the study is unknown. Although the ethical foundation for substituted judgment is firmly rooted in cultural perceptions of personal autonomy,[15] further work is needed to identify the conditions under which "substituted judgments" are, indeed, accurate.

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Public Health and Preventive Medicine

Injury Mortality in New Mexico's American Indians, Hispanics, and Non-Hispanic Whites, 1958 to 1982

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This is one of a series of articles from western state public health departments.

New Mexico has extraordinarily high injury mortality rates. To better characterize the injury problem in New Mexico, we calculated proportionate injury mortality and age-adjusted and age-specific injury mortality rates for the state's 3 major ethnic groups—American Indians, Hispanics, and non-Hispanic whites. According to death certificate data collected from 1958 to 1982 and US population census figures, age-adjusted mortality rates for total external causes varied widely between the sexes and among the ethnic groups. Males in each ethnic group consistently had higher average annual age-adjusted external mortality rates than females. Injury mortality rates for American Indians of both sexes were 2 to 3 times higher than those for the other New Mexico ethnic groups. Motor vehicle crashes were the leading cause of death from injury for all 3 groups. Homicide accounted for twice the proportion of injury death in Hispanic compared with non-Hispanic white males (12.5% and 6.1%, respectively), while the proportion of males dying of suicide was highest in non-Hispanic whites. Deaths from excessive cold and exposure were leading causes of injury mortality for American Indians, but these causes were not among the leading causes of injury mortality for Hispanics or non-Hispanic whites. We conclude that the minority populations in New Mexico are at high risk for injury-related death and that the major causes of injury mortality vary substantially in the state's predominant ethnic populations.

(Sewell CM, Becker TM, Wiggins CL, et al: Injury mortality in New Mexico's American Indians, Hispanics, and non-Hispanic whites, 1958 to 1982. West J Med 1989 Jun; 150:708-713)

In recent years, injury has been increasingly recognized as a major national public health problem, being associated with significant morbidity and mortality and consuming substantial proportions of health expenditures.[1] More than 140,000 Americans die of injuries each year, and 70 million suffer nonfatal injuries.[2,3] Direct and indirect costs associated with injuries in the United States have been estimated at $75 to $100 billion per year.[1] In the United States, injuries rank as the fourth leading cause of death at all ages and as the leading cause of death for persons aged 1 to 44 years.[4] While motor vehicle crashes account for the majority of injury mortality, other causes—such as falls, drowning, fires, poisoning, homicides, and suicides—also account for a substantial loss of life.

New Mexico has the second highest injury mortality rate in the nation; only Alaska's rate is higher.[5] In 1985 the New Mexico death rate for all injuries almost doubled the US death rate (94.4 versus 58.1, respectively, per 100,000 population).[6] New Mexico's motor vehicle fatality rate, consistently among the nation's highest for all states since 1950,[7] makes a large contribution to the state's high injury mortality rate. New Mexico, however, is also burdened by high injury mortality rates from many other causes, including both unintentional and intentional (homicide and suicide) injuries.[8-12]

The epidemiology of many diseases has been shown to differ among members of New Mexico's three major ethnic groups—American Indians, Hispanics, and non-Hispanic whites. Although infectious and chronic disease mortality rates have been shown to vary substantially among the state's major population groups,[13-15] the epidemiology of injury mortality has not been adequately examined. Some published data indicate that Hispanics have higher injury mortality rates than non-Hispanic whites in the Southwest.[6,8,9,12] In addition, southwestern American Indians, who comprise about a tenth of the state's population, have injury mortality rates that far exceed those for US whites.[6,8,16-18] The specific

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causes of injury mortality in these minority groups have not been well characterized, and most reports have been limited by short observation periods.

To better characterize the total injury problem in New Mexico, we calculated proportionate injury mortality and age-adjusted and age-specific injury mortality rates for New Mexico's American Indians, Hispanics, and non-Hispanic whites for the years 1958 to 1982. This report summarizes the descriptive epidemiology of injury mortality in New Mexico over this 25-year period.

Methods

We obtained coded death certificate data for New Mexico residents for the years 1958 to 1982 from the New Mexico Bureau of Vital Statistics. The cause of death was coded according to the seventh revision of the *International Classification of Diseases* (ICD) for the years 1958 to 1968,[19] the eighth ICD revision for the years 1969 to 1978,[20] and the ninth ICD revision for the years 1979 to 1982.[21] Deaths were assigned to accidents and other external causes if coded as E800 to E999.9 for ICD-7, ICD-8, and ICD-9. Because many cause-specific codes changed from ICD-7 to ICD-9, a list of the appropriate ICD codes for each revision (and time period) was prepared and used for subsequent analyses (Table 1).

Ethnicity was assigned by the Bureau of Vital Statistics on the basis of information contained on individual death certificates. Hispanic ethnicity was determined on the basis of the decedents' surnames, the surnames of the decedents' parents, and from specific statements on the death certificate. American Indians were identified solely on the basis of information cited on the death certificate. Non-Hispanic whites were persons whose race was coded as white and who did not have a Spanish surname or other information to indicate that they were Hispanic. We did not examine injury mortality among blacks or other ethnic or racial groups because of the small number of deaths. These exclusions accounted for only 3% of New Mexico's population.

The validity of this approach for classifying ethnicity has not been formally evaluated by the Bureau of Vital Statistics. Therefore, we validated the assignment of ethnicity by comparing the ethnicity of lung cancer patients as stated in their responses to ethnic identification questions in a case-control study[22] with death certificate classification by the Bureau of Vital Statistics. We found 96.4% agreement between self-identification of Hispanic ethnicity and the coding of ethnicity on 221 death certificates and 98.3% agreement between self-identification as non-Hispanic white and the coding on 291 death certificates.

Denominators were derived from the censuses of 1960,[23-25] 1970,[26-28] and 1980.[29] Estimates of the American Indian population for 1960 were adjusted to account for systematic errors that occurred in data processing.[25] The Hispanic white populations for 1960 and 1970 were adjusted to account for different enumeration procedures from 1960 through 1980.

In the censuses of 1960, 1970, and 1980, the US Census Bureau employed different techniques to identify Hispanic ethnicity.[24,26,29] Based on a survey of Hispanics in New Mexico,[30] we adjusted the estimates of the Hispanic populations from the 1960 and 1970 censuses to establish comparability with the 1980 census of the Hispanic population.

To better present the magnitude of the problem of injury-related mortality in New Mexico, we focused on proportionate mortality for each ethnic group. Age-specific and age-adjusted mortality rates were also calculated for five-year periods—1958 to 1962, 1963 to 1967, 1968 to 1972, 1973 to 1977, and 1978 to 1982. Age-adjusted rates were calculated by the direct method and standardized to the 1970 US standard population. The analyses were done with standard software packages from the Statistical Analysis System.[31]

TABLE 1.—*Cause-Specific* International Classification of Diseases *(ICD) Codes for Injury-Related Events, 1958 to 1982*

Cause	*ICD 7th 1958-1968*	*ICD 8th 1969-1978*	*ICD 9th 1979-1982*
Total external	E800-962	E800-949	E810-949
Traffic crashes	E810-825	E810-819	E810-819
Homicide	E964, E980-983	E960-969	E960-969
Suicide	E963, E970-979	E950-959	E950-959
Falls	E900-904	E880-887	E880-888
Drowning	E929	E910	E910
Poisoning	E870-888	E850-869	E850-866
Aspiration of food	E921	E911	E911
Fires and burns	E916	E890-899	E890-899
Airplane crashes	E860-866	E840-845	E840-845
Firearms (accidental)	E919	E922	E922
Excessive cold	E932	E901	E901
Exposure or neglect	E933	E904	E904
Struck by falling object	E910	E916	E916

Results

Age-adjusted mortality rates for total external causes varied widely between the sexes and among the three major ethnic groups in New Mexico (Figures 1 and 2). Males of all ethnic groups consistently had higher average annual age-adjusted mortality rates than females. Among males, American Indians consistently had the highest rates, followed by Hispanics and non-Hispanic whites. American Indian females also had the highest injury mortality rates, with lower rates in non-Hispanic whites and similar rates in Hispanics. The mortality rates for American Indians of both sexes were typically two to three times higher than those for the other New Mexico ethnic groups. Mortality rates in American

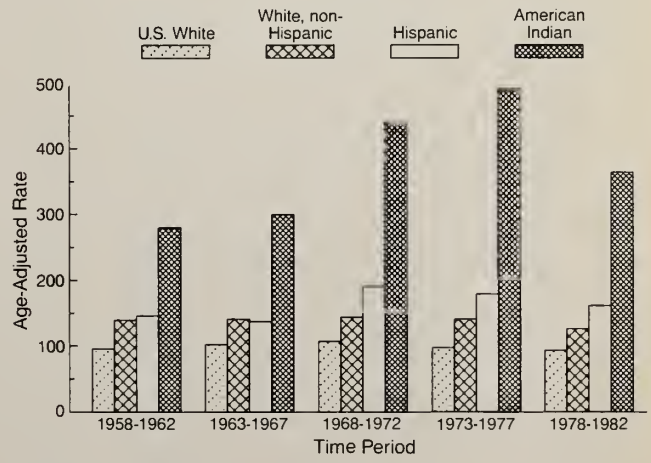

Figure 1.—The graph shows the average annual age-adjusted mortality rate per 100,000 population from total external causes in American Indian, Hispanic, and non-Hispanic white men and boys in New Mexico, 1958 to 1982. The rates for US whites are from the mid-year of the interval.

Indians were two to five times higher than age-adjusted external mortality rates in US whites within comparable time periods.

Of the ten leading causes of external mortality in the years 1958 to 1982 for New Mexico, motor vehicle crashes were the leading cause of external mortality for all three ethnic groups (Tables 2 and 3). Nonetheless, substantial differences in the remaining causes of external mortality occurred among the three ethnic groups. Homicide, suicide, falls, drowning, and fire- and burn-associated deaths accounted for large numbers of deaths for both sexes in all ethnic groups. Homicide accounted for twice the proportion of external causes of death in Hispanics compared with non-Hispanic white men (12.5% and 6.1%, respectively). In non-Hispanic white men, almost 20% of the deaths from external causes were from suicides, a much larger proportion than in Hispanic (11.6%) and in American Indian (10.0%) men. While airplane crashes accounted for 4.2% of non-Hispanic white male deaths and were the fifth ranking cause of external mortality in this ethnic group, airplane crash-related mortality did not appear in the ten leading causes of external death for American Indian or Hispanic males. Among American Indians, deaths due to excessive cold and exposure or neglect were important causes of mortality, while these conditions were not among the ten leading causes for Hispanics or for non-Hispanic whites. When excessive cold and exposure or neglect categories were combined, the resulting combination was the third and fourth leading cause of external mortality for American Indian males and females, respectively.

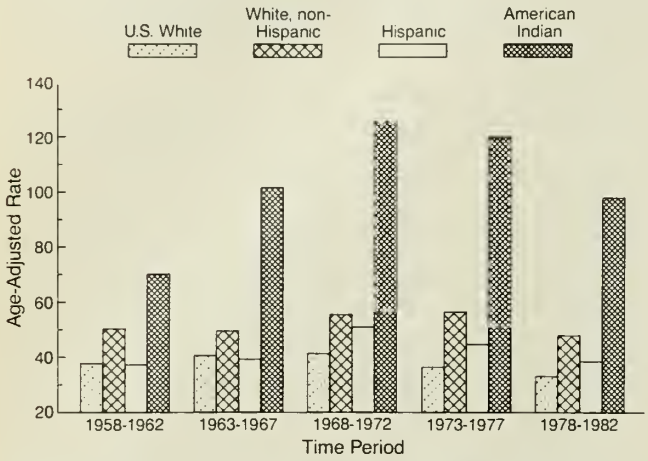

Figure 2.—The graph shows the average annual age-adjusted mortality rate per 100,000 population from total external causes in American Indian, Hispanic, and non-Hispanic white women and girls in New Mexico, 1958 to 1982. The rates for US whites are from the mid-year of the interval.

Mortality rates for males in the 15- to 44-year age group due to external causes are presented by five-year time periods in Table 4. We examined the rates for males in this age range because injuries were the predominant cause of death in this group, and the rates changed rapidly over time. The rates for women, children, and persons older than 45 years were much lower and generally stable across all time periods.

TABLE 2.—*Leading Causes of Injury Mortality for American Indian, Hispanic, and Non-Hispanic White Males in New Mexico, 1958 to 1982*

	Ethnic Group					
Rank	*American Indians*	*No. (%)*	*Hispanics*	*No. (%)*	*Non-Hispanic Whites*	*No. (%)*
1	Traffic crashes	1,496 (47.4)	Traffic crashes	3,200 (42.3)	Traffic crashes	3,621 (36.5)
2	Suicide	316 (10.0)	Homicide	946 (12.5)	Suicide	1,948 (19.7)
3	Homicide	256 (8.1)	Suicide	875 (11.6)	Falls	627 (6.3)
4	Excessive cold	171 (5.4)	Drowning	348 (4.6)	Homicide	603 (6.1)
5	Drowning	163 (5.2)	Falls	315 (4.2)	Airplane crashes	413 (4.2)
6	Exposure or neglect	112 (3.5)	Poisoning	250 (3.3)	Fires and burns	306 (3.1)
7	Falls	103 (3.3)	Fires and burns	213 (2.8)	Drowning	303 (3.1)
8	Aspiration of food	63 (2.0)	Firearms (accidental)	186 (2.5)	Firearms (accidental)	252 (2.5)
9	Poisoning	58 (1.8)	Aspiration of food	150 (2.0)	Poisoning	175 (1.8)
10	Fires and burns	21 (0.7)	Struck by falling object	116 (1.5)	Aspiration of food	156 (1.6)
	Other unintentional injury	399 (12.6)	Other unintentional injury	969 (12.8)	Other unintentional injury	1,506 (15.2)
Total		3,158 (100.0)		7,568 (100.0)		9,910 (100.0)

TABLE 3.—*Leading Causes of Injury Mortality for American Indian, Hispanic, and Non-Hispanic White Females in New Mexico, 1958 to 1982*

	Ethnic Group					
Rank	*American Indians*	*No. (%)*	*Hispanics*	*No. (%)*	*Non-Hispanic Whites*	*No. (%)*
1	Traffic crashes	535 (50.7)	Traffic crashes	819 (41.0)	Traffic crashes	1,384 (35.2)
2	Homicide	92 (8.7)	Falls	202 (10.1)	Suicide	667 (17.0)
3	Fires and burns	56 (5.3)	Homicide	193 (9.6)	Falls	656 (16.7)
4	Falls	48 (4.5)	Suicide	178 (8.9)	Homicide	285 (7.2)
5	Suicide	37 (3.5)	Drowning	97 (4.8)	Poisoning	132 (3.4)
6	Excessive cold	29 (2.7)	Fires and burns	96 (4.8)	Fires and burns	128 (3.2)
7	Drowning	28 (2.7)	Aspiration of food	85 (4.2)	Aspiration of food	97 (2.5)
8	Aspiration of food	21 (2.0)	Poisoning	71 (3.6)	Drowning	87 (2.2)
9	Exposure or neglect	19 (1.8)	Firearms (accidental)	28 (1.4)	Airplane crashes	55 (1.4)
10	Poisoning	15 (1.4)	Struck by falling object	5 (0.2)	Firearms (accidental)	32 (0.8)
	Other unintentional injury	176 (16.7)	Other unintentional injury	224 (11.2)	Other unintentional injury	406 (10.3)
Total		1,056 (100.0)		1,998 (100.0)		3,929 (100.0)

Discussion

We have examined the injury mortality experience in New Mexico over a 25-year period. During this period, age-adjusted external mortality rates for males among New Mexico's three principal ethnic groups exceeded the external mortality rates for US white males (Figure 1). While the rates for American Indians overshadowed those in all other ethnic groups, injury mortality rates in New Mexico's Hispanic and non-Hispanic white males were also well above rates observed nationally for white males. Age-adjusted external mortality rates in females showed a pattern similar to those in males, even though the rates were well below male rates (Figure 2). As was observed among males, mortality rates for American Indian females far exceeded rates among females in the other ethnic groups. These ethnic differences in injury mortality may be partially due to differences in economic status.[5]

Mortality from injuries is a serious health problem in New Mexico. Injuries are the third ranking cause of death in the state and the leading cause of years of potential life lost before age 65. Nationally, injury deaths account for more than 40% of years of potential life lost before age 65[32]; in New Mexico, the proportion of years of potential life lost resulting from injury is even higher (45%).[33] Unintentional injuries accounted for most of the injury mortality in New Mexico from 1958 to 1982. Motor vehicle crashes were the leading cause of injury mortality in all of New Mexico's principal ethnic groups (Tables 2 and 3). This pattern is consistent with injury mortality patterns found nationally and shows the importance of motor vehicle crashes as the single leading cause of preventable death. The proportion of external mortality due to motor vehicle crashes varied from a low of 36% in non-Hispanic whites to almost 50% of external mortality in American Indians. While motor vehicle fatality rates have been declining in New Mexico for many years, these rates remain well above the national figures.[34] Motor vehicle crashes in New Mexico are frequently related to alcohol consumption—55% to 65% of all motor vehicle fatalities involve alcohol.[34] Although data on the proportion of alcohol-involved vehicle fatalities from other states are scant, New Mexico is thought to have one of the highest proportions in the nation (Howard Graff, MS, New Mexico Traffic Safety Bureau, oral communication, June 1988). A disproportionately high use of alcohol among American Indians in New Mexico may contribute to their elevated motor vehicle mortality rates compared with Hispanics and non-Hispanic whites.[35]

Falls, drowning, poisoning, and fire and burns were among the ten leading causes of external mortality for both sexes and all ethnic groups. Airplane crashes accounted for a small proportion of deaths in non-Hispanic whites, but this cause of death was not among the ten leading causes for either American Indians or Hispanics. This ethnic pattern is probably related to the generally lower economic status of American Indians and Hispanics, with the resultant lack of opportunity to fly small aircraft. Deaths related to the combined categories of excessive cold and exposure or neglect were the third and fourth ranking causes of external deaths in American Indian males and females, respectively, but these causes of death were not among the ten leading causes for either Hispanics or non-Hispanic whites. A previous study in New Mexico has shown a high rate of American Indian deaths due to excessive cold and exposure or to pedestrians being struck by motor vehicles.[36] Alcohol use was a major risk factor in these deaths. A smaller number of deaths occurred in all ethnic groups from the aspiration of food. The proportions of deaths caused by aspirating food have declined substantially in the past several years. It is not clear what factors might have influenced this decrease.

Intentional injuries (homicide and suicide) accounted for

TABLE 4.—*Age-Specific Mortality Rates per 100,000 Population From Total External Causes in American Indian, Hispanic White, and Non-Hispanic White Males in New Mexico, 1958 to 1982*

Age Group, yr	*Ethnic Group*	*1958-1962*	*1963-1967*	*1968-1972*	*1973-1977*	*1978-1982*
15-19	American Indian	223.1	135.8	419.4	476.7	373.7
	Hispanic	157.4	151.6	215.1	225.5	172.3
	Non-Hispanic white	115.5	131.8	168.3	186.8	155.2
	US white	88.5	99.4	116.1	117.1	121.3
20-24	American Indian	406.5	420.1	634.2	871.9	662.1
	Hispanic	243.8	212.9	342.7	307.7	317.2
	Non-Hispanic white	160.9	154.1	185.1	235.2	220.0
	US white	118.1	133.9	156.1	150.6	160.7
25-29	American Indian	513.3	465.2	534.3	821.7	538.3
	Hispanic	183.7	160.2	250.9	262.6	280.0
	Non-Hispanic white	174.5	129.7	149.4	156.2	184.5
	US white	93.1	106.6	120.5	122.0	134.0
30-34	American Indian	380.5	323.8	492.6	536.2	381.0
	Hispanic	174.1	111.0	240.6	220.7	248.9
	Non-Hispanic white	183.6	137.0	125.0	164.9	143.2
	US white	82.2	95.7	106.5	100.7	108.1
35-39	American Indian	362.9	370.1	553.7	765.2	470.2
	Hispanic	138.1	135.8	194.6	231.3	232.8
	Non-Hispanic white	169.3	153.7	133.3	131.7	154.1
	US white	84.6	95.8	105.7	99.7	97.8
40-44	American Indian	325.3	378.7	509.3	525.7	531.3
	Hispanic	125.4	127.1	215.4	219.9	180.8
	Non-Hispanic white	183.5	164.4	165.6	116.2	119.9
	US white	90.0	98.5	108.0	98.7	94.5

substantial proportions of the external mortality in all of the state's ethnic groups. The high proportion of suicides in non-Hispanic whites contrasts sharply with the proportion of external deaths due to suicide in American Indians and Hispanics. Nonetheless, high suicide rates have been reported among New Mexico's young American Indian men,[37] especially among the Apaches. The high proportion of deaths in Hispanics due to homicides exceeded that of American Indians and non-Hispanic whites. In the Southwest, homicide rates among young Hispanic men triple the rates for non-Hispanic white men.[38] Data from the New Mexico Office of the Medical Investigator show that about half of the homicides and suicides in the state in 1985 were associated with alcohol use (alcohol detected at a blood concentration of greater than 0.005%).[39] In addition, data from the Office of the Medical Investigator point to the central role of firearms in homicides and suicides in New Mexico. In all, 48% of the homicides and 54% of the suicides in New Mexico in 1985 involved the use of firearms.[39]

Alcohol abuse is a major public health problem and a strong contributor to injury mortality in New Mexico. According to the National Institute on Alcohol Abuse and Alcoholism, New Mexico ranks second in the nation, after Nevada, in the rate of alcohol-related mortality.[40] Studies have shown that the rates in New Mexico far exceed national rates for causes of death that are completely attributable to alcohol use—that is, alcoholic psychoses, the alcohol dependence syndrome, nondependent abuse of alcohol, alcoholic liver disease, alcoholic cardiomyopathy, alcoholic polyneuropathy, alcoholic gastritis, and accidental poisoning with alcohol.[41] Mortality rates directly attributable to alcohol use among New Mexicans are nearly twice the rates in the US population as a whole, and among New Mexicans, alcohol-related mortality rates in American Indians and Hispanics far exceed the rates in non-Hispanic whites. In the 15- to 24-year-old age group, the mortality rate attributable to alcohol use is 50 times greater in American Indians compared with non-Hispanic whites, and the mortality rate for Hispanics is 5 times higher than among non-Hispanic whites in the state.

Long-term temporal improvements in emergency medical response, transport, and care have undoubtedly improved survival for injuries that would have proved fatal only a few years ago. The implementation of regional trauma systems elsewhere has resulted in substantially improved trauma care and reduced death rates due to trauma.[42] New Mexico has only recently implemented an organized, regional trauma care system, and its effect on injury mortality has not been evaluated. Decreases in fire- and burn-associated deaths have been shown to be related to dramatic improvements in burn care.[43]

Possible limitations and biases in this study include the misclassification of the cause of death, age, sex, year of death, and ethnic status. Age, sex, and year of death were likely to have been misclassified only rarely. Misclassifying the cause of death from injury is probably much less common than misclassifying for many other causes of death, however, as most injury-related deaths occur within a short period of time following a traumatic event.[5] Misclassifying the ethnic group may have affected our calculations of ethnic-specific rates. For the numerators of the mortality rates, ethnicity was assigned by the New Mexico Bureau of Vital Statistics with procedures that were constant over the study period. The designation of American Indian on the basis of stated race or death certificate information should closely parallel the self-identification of race used by the US Census Bureau, on which our denominators were based. Separating Hispanic whites from non-Hispanic whites is more of a potential problem. For Hispanics, the Bureau of Vital Statistics considered surname and parents' surnames as well as statements on the death certificates. We did, however, find a high level of concordance (greater than 96%) between self-reported Hispanic-white ethnicity among subjects who participated in a statewide case-control lung cancer study from 1980 through 1982[22] and the code assigned by the Bureau of Vital Statistics to deceased subjects. This observation suggests that the misclassification of Hispanics was not a major source of bias in the study.

Because most injuries are preventable, we conclude that a substantial loss of life could be prevented in New Mexico if high-risk groups were targeted and appropriate intervention strategies developed to reduce the number of unnecessary injury-related deaths. Additional measures to increase seatbelt use and decrease the incidence of driving while intoxicated are priorities. Studies examining the risk of mortality in New Mexico from motor vehicle crashes, homicide, suicide, drowning, falls, and excessive cold or exposure are warranted.

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Medicine and Law

Physicians' Attitudes Toward the Legalization of Marijuana Use

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We asked 303 practicing physicians in general internal medicine, family medicine, gastroenterology, or psychiatry to indicate whether possessing or using marijuana should be considered a felony, a misdemeanor, warrant the issuance of a citation, or be legalized. The position physicians advocated was unrelated to their specialty, experience diagnosing or treating substance abuse problems, their attitudes toward the efficacy of the treatment of drug abuse, or any other work role or habit we measured. Legalization or citation as compared with harsher penalties, however, was more likely favored by physicians who were younger, less religious, politically more liberal, and those less likely to perceive a serious drug problem in society. Legalization was also more likely favored by physicians who themselves had used marijuana, cocaine, and amphetamines but was unrelated to the use of alcohol, cigarettes, or tranquilizers. Although physician opinion should be sought as society deals with the drug problem, this study suggests how physicians' characteristics may influence the opinions that are rendered.

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As the decade of the 1980s comes to a close, there is general agreement that the United States has failed to develop an effective policy for reducing or controlling the use of illegal drugs by its citizens. Government efforts toward reducing the demand for drugs through educational campaigns such as "Just Say No" to drugs, dramatic punitive law enforcement efforts such as "Zero Tolerance" in which expensive automobiles or boats have been confiscated if their owners were caught possessing as little as less than an ounce of marijuana, or the testing for drug use in the workplace have not worked sufficiently. The government also has tried to control the supply side of the drug problem by indicting drug kingpins in countries that export large quantities of illegal drugs to the United States; increasing search-and-seizure procedures of people, cars, boats, and airplanes at United States points of entry; burning fields of marijuana and coca leaves; and proposing to employ the military in fighting the "war on drugs." With none of these attempts appearing to be notably effective in reducing the demand for or the supply of drugs, some politicians, law enforcement officials, and others have proposed another possible solution to the drug problem: legalize their use. Several national magazines have recently debated the pros and cons of legalization, and hearings have been conducted to learn more about the potential of such a policy.

Although the opinions of many segments of society should be solicited regarding legalizing drugs, one critical group ought to be physicians. Medical opinion and expertise should play an important role in the adoption or rejection of policies to legalize some or all currently illegal drugs. Yet little or no systematic information exists on how physicians view the US drug problem or possible solutions.[1-5]

Our purposes in carrying out this research were to describe physicians' attitudes toward the legal status of commonly used drugs and to explore factors associated with the positions that physicians take on the legalization issue, focusing on marijuana. In this regard, we tested a model in which we hypothesized that physicians' positions on the legal status of marijuana were associated with their demographic and social characteristics, their work habits and roles, their attitudes toward the US drug problem, their political and religious beliefs, and their current and previous use of alcohol and drugs.

Methods

Sample and Design

Questionnaires were mailed during the summer of 1987 to all full-time academic physician faculty members of the departments of medicine and psychiatry at the University of California, Los Angeles, and to all community-based clinical faculty affiliated with those departments in private practice whose specialty was general internal medicine, family medicine, gastroenterology, or psychiatry. Because of the sensitive nature of some questions, respondents were assured confidentiality and anonymity. Questionnaires were sent to all physicians twice, one month apart, because our research design included fully anonymous responses and did not permit a determination of which physicians had responded to the initial mailing. Of the 629 questionnaires sent, 21 were returned by the post office. Of the 608 re-

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maining surveys, 303 were completed and returned, constituting a 50% response rate.

Physician respondents had the following characteristics: their average age was 48 years, 91% were white, 87% were men, 85% were married, 39% were academically based full-time faculty, and 61% were in private practice. About half were board certified in internal medicine, 24% in psychiatry, 14% in family medicine, and 12% were not board certified. Based on our initial mailing rosters, nonrespondents were somewhat more likely to have been in community-based practices than in the academic setting. No differences in specialty or sex were found among respondents and nonrespondents. Also, the average age of respondents was similar to the age of respondents in a survey previously conducted in the same physician population in which a considerably higher response rate was attained.[6]

Legalization of Drugs

Although the major part of this report will focus on physicians' attitudes toward the legalization of marijuana, respondents were also asked to describe their views on the use of cocaine, LSD, heroin, amphetamines, or diazepam (Valium) without a prescription. They were asked to check one of four responses, regardless of current law, with respect to their views concerning what legal actions should be taken for the possession or use of each substance: (1) make it legal; (2) issue a citation with a fixed fine, like a parking ticket; (3) make possession or use a misdemeanor; or (4) make it a felony.

Other Measures

As part of our research, we ascertained the physicians' age, sex, race, marital status, religion, political orientation or party affiliation (or both), family size, and the degree to which respondents considered themselves to be religious persons (religiosity). For work roles and habits, we asked about hours worked per week; vacation time taken; volume of clinical work; location and type of practice; board certification; specialty; and involvement in teaching, research, administrative, and patient care activities. We also asked physicians to report on how frequently they had seen patients with drug or alcohol problems in the past year and how frequently they counseled, treated, or referred such patients for treatment.

In addition, we also explored various drug-related attitudes. We administered a four-item scale of attitudes toward the US drug problems ($\alpha = .57$), a four-item scale of attitudes toward the appropriateness of physicians diagnosing and treating drug problems in their patients, and two previously validated scales created by Chappel and co-workers that measured attitudes toward treatment.[7] Finally, we also ascertained the physicians' current and previous use of cigarettes, alcohol, marijuana, cocaine, amphetamines, and mild tranquilizers.

TABLE 1.—*Physicians' Attitudes Toward Legalizing Commonly Used and Abused Drugs (n=303)*

	Position on Drug Use, % Yes			
Drug	*Legalize*	*Citation*	*Misdemeanor*	*Felony*
Marijuana	41	25	30	4
Cocaine	12	5	34	49
LSD	11	7	31	51
Heroin	10	4	25	61
Amphetamines	10	13	46	30
Mild tranquilizers	15	25	48	12

Results

Although the focus of our attention in this report is on marijuana, Table 1 shows the attitudes of our physician sample toward the six substances we evaluated. Clearly the physicians viewed the issue of legalization differently for each of the six substances. For example, only a third of the sample favored a misdemeanor or felony status for possessing or using marijuana whereas a considerable majority favored such strict penalties for possessing or using cocaine (83%), LSD (82%), heroin (86%), and amphetamines (76%). Less stringent penalties were recommended for the use of mild tranquilizers.

Relationships between physicians' opinions regarding the legal status of marijuana and their personal and professional characteristics were determined by using a one-way analysis of variance for continuous variables and χ^2 tests for discrete variables. Because of the large number of significance tests done, the criterion set for statistical significance in the ensuing analyses was P less than .01.

With respect to sociodemographic characteristics, we found no relationships between physicians' views about the legal status of marijuana and their sex, religion, family size (number of children), marital status, or race. As shown in Table 2, however, physicians who favored legalization or a citation status were, on average, five years younger than those favoring a misdemeanor or felony status.

Practice characteristics and work habits were also unrelated to attitudes toward legalization. No relationships were found between such attitudes and hours worked per week; the number of vacation days taken in the past year; the amount of time spent in primary versus specialty patient care; scholarly productivity measured by articles published; medical specialty; board certification status; how physicians divided their time among administrative responsibilities, research, teaching, and patient care; or the number of outpatients seen in the previous two weeks. None of our measures

TABLE 2.—*Physicians' Attitudes Toward Legalizing Marijuana in Relation to Age, Attitudes Toward the Seriousness of the US Drug Problem, and Religiosity*

	Position on Marijuana Use, means				
Physician Characteristic	*Legalize*	*Citation*	*Misdemeanor*	*Felony*	*F*
Age, yr	46.2	45.2	51.2	50.3	4.61*
Perceived seriousness of the US drug problem†	3.8	4.0	4.2	4.6	7.29‡
Religiosity§	4.1	3.7	3.4	2.8	13.76‡

*ANOVA=$P<.01$.
†Not serious=1; serious=5.
‡ANOVA=$P<.0001$.
§Religious=1; not religious=5.

reflecting the nature or degree of experience in treating patients with alcohol or drug problems over the past year were related to physicians' attitudes toward legalization.

Regarding attitudes, physicians' views about the efficacy of treating substance abuse problems and their views about the appropriate role of physicians in drug treatment were unrelated to their views on legalizing marijuana. Physicians who perceived the US drug problem to be more serious, however, were more likely to have endorsed a misdemeanor or felony status for the possession or use of marijuana than physicians who perceived the drug problem to be less serious (Table 2). Regarding attitudes toward religion and politics, physicians who rated themselves as less religious were significantly more likely to favor legalization or a citation. More religious physicians favored a misdemeanor and felony status. Also, Table 3 shows that physicians who considered themselves to be politically liberal were more likely to favor legalization than were politically conservative physicians, who favored harsher penalties. Similarly, physicians who identified themselves as Democrats or Independents were more likely to favor a legal or citation status for marijuana use than were Republicans, who favored harsher penalties.

Finally, we explored the relationship between physicians' current and previous use of alcohol, cigarettes, and selected mood-altering drugs and their attitudes toward the legalization of marijuana. Attitudes on legalization were unrelated to the frequency of the physicians' current use of beer, wine, or liquor and were unrelated to their current or past use of cigarettes or mild tranquilizers. As shown in Table 3, however, physicians who had sometime in their lives used marijuana—55% of the sample, with 9% being current users—were more likely to favor less harsh or no penalties for marijuana use than those physicians who had never smoked marijuana. Identical patterns were found among the 15% of physicians who had tried cocaine and among the 26% who had tried amphetamines (Table 3).

Discussion

Because physicians are familiar with the scientific method of inquiry, read the scientific literature, and are primarily responsible for treating the health problems of the general population, they represent one of the occupational groups that should most be able to assess the effects of drug use on the health of our society. Their opinions are important and should be taken into account in formulating any policy regarding how illegal drug use should be handled by society. In addition, because the use of marijuana has been a visible part of American life since the 1960s, most contemporary physicians, including those whose opinions on legalization we studied, have probably had considerable experience with marijuana use or marijuana users on either a personal or a professional basis. More than half of our respondents had actually tried marijuana, and probably many more had known occasional users in college, medical school, or residency training. Others undoubtedly treated patients who smoked marijuana, and still others may have dealt with issues concerning marijuana use during the normal course of raising their own children.

An analysis of our data has indicated that the attitudes of physicians toward the legalization of marijuana use were not related to the nature of their practices or clinical experience but rather to personal factors such as using marijuana, current attitudes toward the drug problem, their religious feelings, and current political orientations. Neither their reported frequency or type of clinical experience with substance abuse problems over the past year nor their attitudes toward the efficacy of drug treatment were related to their positions on legalization. Also, none of the many work roles or involvements we studied were related to physicians' positions on legalization.

Thus, if policymakers intend to seek physician opinion on the legalization issue, the selection of exactly which physicians to testify will become critical. Because opinion in our study was unrelated to clinical or scientific credentials, the process of choosing physicians as expert witnesses may prove similar to the process of choosing experts in any field in which facts are heavily interpreted through surroundings, beliefs, and opinions. When dealing with controversial moral or ethical issues that may bear on the development or implementation of legislative policy, physicians behave much

TABLE 3.—*Physicians' Attitudes Toward Legalizing Marijuana in Relation to Their Political Orientation and Party Affiliation and Their Previous Experience With Marijuana, Cocaine, and Amphetamines*

	Position on Marijuana Use, % Yes				
Physician Characteristic	*Legalize*	*Citation*	*Misdemeanor*	*Felony*	χ^2
Political Orientation					
Liberal	53	23	22	2	...
Middle-of-the-road	34	29	34	3	27.26, 6 *df*
Conservative	22	24	41	13	$P<.0001$
Political Party Affiliation					
Strong Democrat	51	24	20	4	...
Weak Democrat	43	30	27	0	...
Independent	47	24	27	2	...
Weak Republican	19	19	50	11	37.00, 12 *df*
Strong Republican	6	28	50	17	$P<.0001$
Past Substance Use					
Used marijuana	52	28	19	1	29.77, 3 *df*
Never used marijuana	28	22	42	8	$P<.0001$
Used cocaine	60	29	11	0	13.32, 3 *df*
Never used cocaine	37	25	33	5	$P<.01$
Used amphetamines	56	23	21	0	12.40, 3 *df*
Never used amphetamines	36	26	32	6	$P<.01$

like any other group of citizens. Thus, in putting together panels of physician experts to develop or recommend policies on legalizing drugs, extreme care must be taken to select a balanced representation from the entire political and religious spectrum, rather than to rely exclusively on physicians from any particular specialty, research background, or stated expertise in diagnosing and treating substance abuse. Furthermore, those evaluating the physicians' testimony will have to give special attention to the professional *and* personal sources from which each physician's opinion about legalization is derived.

Finally, the diverse attitudes of physicians toward the legalization of the limited number of drugs we studied (Table 1) clearly suggest that neither legalization nor harsher penalties can represent blanket solutions to the problems of substance abuse. From the perspective of the physicians in our sample, however, the decriminalization of marijuana—but not of other illegal or controlled substances—was strongly preferred.

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Methadone Maintenance

METHADONE MAINTENANCE is, I think, very useful for people who have tried other ways to stop using heroin. In San Francisco, we are preferentially admitting opiate addicts infected with the human immunodeficiency virus (HIV) into methadone treatment to get them out of the pool of needle sharers because at this point there is still a small proportion of addicts who are HIV positive, and it is important to pull those people into treatment so that they will not share needles and spread their HIV.

—STEVEN L. BATKI, MD

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Information

An Example of Hospital Utilization Review

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UTILIZATION REVIEW IS REQUIRED of all acute care hospitals expecting to be certified by the Joint Commission on Accreditation of Healthcare Organizations or to receive payment from the federal government for providing care to persons covered by Medicare.[1] Utilization review is also required by other third-party payers of hospital care, including private insurers and the state of California, for those patients covered under the state's Medi-Cal (Medicaid) program. While the fundamental utilization review requirements are basically the same regardless of the insurer, each third party, directly or through its subcontractors, has promulgated specific requirements and criteria for such review.

Although utilization review is often described as having important quality assurance components, the central thrust is cost containment. This presently takes a fairly simple and direct form: the third-party insurer refuses to reimburse a hospital for services rendered to a patient if, according to review of that patient's stay in hospital, the patient did not require either admission to the hospital or continued acute hospital care for one or more days. Because hospital reimbursement by the federal government for Medicare-sponsored patients is now fully based on assignment to diagnosis-related groups (DRGs), the cost-containment aspect of utilization review for those patients should become less prominent, although scrutiny of the need for admission to hospital will continue to be intense. Utilization review for those patients would serve also as a way of monitoring performance, especially directed toward identifying premature discharges of patients, early readmission, and inappropriate restrictions in the use of expensive ancillary services. From a hospital's point of view, utilization review can be valuable—even if it is not required by third-party sponsors—in detecting and monitoring an inappropriate use of services.

The University of California, Davis, Medical Center (UCDMC) is a major teaching hospital, owned by the university, having 441 licensed beds and extensive outpatient, subspecialty, and emergency services. Approximately 15% of its inpatients are Medicare-sponsored, 41% are Medi-Cal-sponsored, and 20% are county-sponsored. In addition, UCDMC is the regional trauma center, providing care to more than 90% of all major trauma victims in the area. The hospital also contains separately licensed and regulated inpatient psychiatry and rehabilitation units.

At UCDMC a formal utilization review process has been in operation for several years. An attempt is made in this process to determine the medical need for admission and the need for further hospital care for each day of every patient's hospital stay, regardless of the third-party payer, if any. This process meets the requirements established by the Joint Commission on Accreditation of Healthcare Organizations, private third-party insurers, and by the federal government for Medicare patients. The results of our hospital's utilization review process for Medicare patients are audited periodically by Medicare's contractor, California Medical Review, Inc (CMRI). Patients covered by Medi-Cal are reviewed independently by staff from the Medi-Cal field office for each of those patients covered by them.

I describe the utilization review process that has evolved in our hospital, provide examples of the kinds of data routinely gathered, and discuss briefly some of the problems and strengths of the process.

The Utilization Review Committee, established by the bylaws of the medical staff, is appointed by the chief of staff with the concurrence of the hospital director. It includes representatives from at least five different clinical departments, the resident medical staff, nursing administration, and hospital management, as well as the utilization review advisory physician and the hospital managers of Clinical Social Services and of Patient Services. The committee has developed and approved a plan for utilization review and from time to time modifies the plan as experience dictates. The committee regularly reviews data regarding the appropriateness of admissions and continued hospital stays. It reviews other data related to lengths of stay, patterns of use of hospital services, and other items that may be referred to it by the medical staff or hospital administration. This committee also has established an appeals subcommittee to review cases where denial of benefits or reimbursement is contested and to determine the merit of appeals.

Actual utilization review is done by the Department of Patient Services using a team of specially trained registered nurses who review on a daily basis the medical records of all patients in hospital on that day. For patients who have been discharged on weekends—when active utilization review does not take place—medical records are retrieved and analyzed on Mondays as though these patients were still in hospital.

The utilization review nurses, designated as Patient Services Coordinators, visit each inpatient nursing unit daily to review the medical charts of each patient present that day. The coordinators compare the medical record with criteria that are relevant to 13 system-specific areas and 1 generic area.[2] Each area contains criteria indicating severity of illness, relating primarily to the need for admission to hospital and intensity of service, relating primarily to the need for continued acute hospital care. All sets of criteria have been reviewed, modified as needed, and accepted by the appropriate clinical departments. The validity of similar sets of criteria, designated the Appropriateness Evaluation Protocol, has been reported.[3,4]

In their review of each medical record, the coordinators specifically note medications and routes of administration, monitoring needs as documented by physicians' orders, pertinent laboratory results, and more subjective components of the record, including nursing notes and, especially, progress notes written by the responsible physicians. If documentation

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ABBREVIATIONS USED IN TEXT

CMRI = California Medical Review, Inc
DRGs = diagnosis-related groups
UCDMC = University of California, Davis, Medical Center

in the medical record is such that none of the criteria are met or if there is serious question, that day of the patient's hospital stay is referred to a physician—the Utilization Review Physician Advisor—for further review. In this way, documentation in the medical record is used in comparison with explicit criteria to identify cases of hospital admission or further acute hospital care that appear questionable. For each day of each patient's hospital stay, the coordinators complete a short work sheet, and these work sheets are retained for further analysis as needed. The coordinators rapidly develop the skills and facility to apply the explicit criteria to cases within one or more specialty areas because the coordinators are typically assigned to the same inpatient nursing services on a prolonged basis.

Referrals to the utilization review advisory physician take place daily, Monday through Friday, when each coordinator submits to the physician advisor the reasons why the admitting of a particular patient or a subsequent day of acute care in hospital does not meet the explicit criteria, based on a review of the record. I wish to emphasize that the criteria, even when modified, are screening criteria and do not serve as standards of care. The physician advisor reviews the work sheet prepared by the coordinator and either approves the admission or continued stay—based on clinical judgment—or, more often, attempts to reach the responsible physician to obtain further information. The physician advisor then determines the appropriateness of the admission or continued stay, with or without the concurrence of the responsible physician. Sometimes, because of an inability to reach the responsible physician, the utilization review physician advisor must make decisions without complete information. If the decision of the physician advisor is that the admission or a day of acute hospital care is not clinically warranted, this result constitutes a denial. All referrals to the physician advisor are listed in a log that includes relevant patient identification data, the date, reasons for referral, the decision of the physician advisor, the reasons for that decision, attempts by the physician advisor to reach the physician responsible for the patient, and whether the responsible physician responded. In the case of denial, the patient and the responsible physician are notified as directed by the requirements of the third-party payer, with a full explanation of appeal options.

The reasons for denial basically reflect the judgment that the studies or services provided to the patient could be reasonably provided on an outpatient basis or in a facility providing a lower level of care, or that such studies or services have been unnecessarily delayed either because of patient compliance or for reasons beyond the control of the patient—equipment failure, for example. In our institution, the basis for denying admissions and continued acute hospital days is exactly the same regardless of the patient's third-party payer, if any. The issuance of denial letters depends on the requirement of the third-party payer, however, and the requirements are most rigid in the case of Medicare sponsorship. For those patients covered by Medi-Cal, institutional utilization review is the same as for other patients, but an additional independent review of these patients is conducted by Medi-Cal staff on a daily basis. Medi-Cal staff are responsible for formally denying further benefits and for notifying the patient of such denial. Our hospital may appeal these denials with Medi-Cal, often using the results of its own utilization review if that result disagrees with the determination by Medi-Cal staff and, in all cases, if the patient's responsible physician supports the appeal.

Table 1 shows the kind of data routinely collected and reported to the hospital administration and to the Utilization Review Committee. Similar reports specific to each clinical service in the hospital are provided to the chair of that service. Table 1 shows the total patient-days for the month in question, the number of patient-days referred to the utilization review physician, and those days for which no need for acute hospital care could be substantiated. These numbers are reasonably representative: typically, 2% to 3% of total patient-days are referred to the utilization review physician, and from a third to two thirds of the referred days are actually denied. Of all patient-days, 1% to 1.5% are denied. The rate of referral and subsequent denial varies greatly by clinical service. The proportion of patient-days referred for those patients in intensive care units, obstetrics and gynecology, the newborn nursery, and some surgical subspecialties tends to be considerably less than the fraction of days referred (and denied) for patients on the internal medicine service, for example.

As indicated, this Utilization Review Activity Summary is reviewed monthly to monitor the number of referred days and denied days both with respect to previous months and to specific inpatient services. Because a reason is assigned for every day referred to the utilization review physician—13 such reasons are codified—and because a reason is also assigned for every day actually denied—out of 11 formalized—it is possible to monitor with time, or by service, specific reasons for questioning each patient-day or admission and for denial. Special reports can be generated to examine whether the reasons for denial have changed, for example, or whether the reasons for the denial of patients on one service are different from those on other services.

Of interest has been the denial of patient-days because of some delay in service—a scheduled surgical procedure is

TABLE 1.—*Summary of Utilization Review Activity, March 1987*

Interval	*Total Patient-Days, No.*	*Patient-Days Referred to Utilization Review Physician, No. (%)*	*Patient-Days Denied, No.**
March 1987	11,947	296 (2.5)	156
February 1987	10,730	304 (2.8)	167
Previous Quarter	34,338	1,003 (2.9)	533

*Includes admissions denied as inappropriate and subsequent denied days.

TABLE 2.—*Utilization Review Report of Delay-of-Service*

Date	*Total Patient-Days, No.*	*Patient-Days Referred to Utilization Review Physician, No.*	*Patient-Days Denied Because of Delay, No. (%)*
October 1986	12,038	467	70 (15)
November 1986	11,485	279	56 (20)
December 1986	11,863	344	48 (14)
Total Quarter	35,386	1,090	174 (16)

TABLE 3.—*Utilization Review Report of Reasons for Delay-of-Service*

Date	Reason: Operating Room Time, No.	Other Procedures, No.	Await Bed,* No.	Medical Indecision, No.	Judicial Decision, No.	Total
October 1986	40	14	0	16	0	70
November 1986	27	5	10†	5	9	56
December 1986	19	5	23	1	0	48
Totals						
This Quarter	86	24	33†	22	9	174
Previous Quarter	69	33	22†	54	9	187
Both Quarters	155	57	55	76	18	361

*Lack of available bed for transfer to a rehabilitation unit.
†Includes delay awaiting special orthopedic equipment.

postponed because of inadequate operating room time, for example, usually the result of an unanticipated influx of trauma patients. A delay of service could also include delays in ordering or providing necessary diagnostic services. The hospital could in theory correct many delays of service, avoiding subsequent denials and potential loss of reimbursement. At UCDMC delays of service are commonly related to an excessive demand for operating room time, equipment breakdown—especially the imaging scanners—and remnants of more leisurely scheduling and staffing patterns, delaying the necessary diagnostic and therapeutic management of patients, especially on weekends, holidays, and off-hours. Of the 611 patient-days referred to the physician advisor in April and May 1986, for instance, 31 (5.1%) were related to delay of service. Of the 31 days, 10 were related to delays in scheduling operating rooms or diagnostic studies, and 14 were related to delays in receiving biopsy reports and in making patient management decisions. During October through December 1986, the number of referrals because of a delay of service increased to 16% of all referrals, related in part to an extremely high inpatient census and an increased number of trauma patients (Table 2). Delays related to the scheduling of procedures accounted for 212 days, of which 155 were due to a lack of operating room time (Table 3). Delays caused by the unavailability of beds, primarily in the separately licensed psychiatry or rehabilitation units, accounted for 55 days, and delays related to late test results or medical indecision amounted to 76 days. Clearly, delay of service totaling more than 700 denied patient-days per year represents a notable inefficiency of hospital operations.

Concern has been expressed regarding the effect of delays on obtaining conservatorships. An analysis of previous utilization review data indicated that delays in obtaining legal conservatorships amounted to 3 to 40 days per month of unwarranted hospital stays—that is, acute hospital care not needed but unavoidable because of a lack of authorization to arrange other dispositions for those patients. This total reflects a smaller but still substantial loss of revenue to the hospital and has resulted in successful efforts to shorten the time required to obtain conservatorships.

There is no external standard by which we can judge the accuracy of our institutional utilization review process. We can, however, compare our in-house results for Medi-Cal-sponsored patients with the results obtained by the on-site Medi-Cal reviewers. In fiscal year 1986-1987 Medi-Cal reviewers denied about 3% of the hospital days of Medi-Cal-sponsored patients. Our process selected about 2.9% of days for review, but only 1.5% were denied. The difference reflects the more stringent criteria for acute hospital care applied by the Medi-Cal staff. When our review indicates that acute hospital care is warranted, the strength of our appeal to approve additional hospital days is increased, and, consequently, we routinely appeal those instances if our review indicates that further hospital care is warranted. Our success rate, unfortunately, is not good, although it would be even worse without the evidence and documentation gathered by our utilization review process.

Possibly more relevant to our process and an assessment of its merit is the result of audits conducted by Medicare's local contractor, California Medical Review, Inc. Because of our ongoing utilization review activity, UCDMC has been granted a waiver by Medicare. Our results are audited monthly, however, along with specific areas of interest to CMRI, such as readmissions and premature discharges, contested assignments of a DRG number, and those cases in which we have issued a denial letter. Representative results of CMRI audits conducted on three occasions early in the 1986-1987 fiscal year show that 33 cases out of 302 reviewed were referred to their physician advisor; of these, 7 (2.3%) were referred because of questions regarding the need for admission, and no cases were referred because of a question regarding the need for continued hospital stay. Of the seven cases referred for admission questions, three were early readmissions, and two of these were probably related to a lack of operating room time during the previous admission.

For several reasons, the number of inappropriate hospital admissions is low. Virtually all patients admitted to UCDMC enter through the emergency department or have had a previous authorization for admission. Of some 9,428 admissions in the last six months of 1987, only 12 were denied by our utilization review process. Three of these denials were caused by the delay of a surgical procedure for patients admitted electively, and eight were denied because they were judged to require care that was appropriate for outpatient or lower level services. The contrast between our finding less than 0.2% inappropriate admissions and the findings noted above by CMRI (7 out of 302) is noteworthy. It reflects mainly Medicare's emphasis on preventing admissions, especially early readmissions, and our institution's packed operating room and procedure schedule, which hinders predictable sequential or staged procedures, resulting in delays or interim discharge and subsequent early readmission.

Similarly, Medi-Cal denials of admissions are substantially greater than our review detects, and, unfortunately, these denials are often retroactive despite the daily review by Medi-Cal staff and preadmission authorizations. Approxi-

mately 1% of the admissions of Medi-Cal patients is denied retroactively by Medi-Cal. Audits by other third-party payers are of less use in assessing the validity of our process.

Discussion

Although important quality of care issues can be detected and monitored by the utilization review process, the major motivation for utilization review is to contain costs. The statistics presented in Table 1 indicate that the utilization review process in our institution finds about 1.5% of the total patient-days to be not medically required. If the timely discharge of medically cleared patients could be achieved, the institution would presumably save as much as 1.5% of its inpatient costs (actual hospital costs incurred in caring for many denied patients will be less than for those truly needing acute care). If delays of service were eliminated or greatly reduced, some 30 to 60 days could be saved monthly.

Previous studies have reported that a much larger proportion of hospital care is medically unnecessary. Using an Appropriateness Evaluation Protocol, 12% to 28% of patient-days were judged medically inappropriate,[5] while a report comparing inappropriate hospital use across six health insurance plans found that 10% to 35% of admissions were inappropriate and more than 30% of hospital days were inappropriate.[6] A 1987 study retrospectively determined that 47% of 4,329 discharges had an inappropriate hospital day—the day before discharge—and that 16.8% of 7,301 admissions were inappropriate.[7]

These figures conflict so drastically with ours and even with independent reviews of our patient records by Medi-Cal and CMRI that a simple explanation seems impossible. All have used the Appropriateness Evaluation Protocol—or similar criteria—so important differences in screening criteria should not exist. It should be pointed out also that many of the previous studies were limited in scope. Payne reviewed only the penultimate hospital day instead of all days,[7] and Kemper reviewed every tenth day.[5] Other studies excluded pediatric, obstetric, or alcoholic patients[6] or otherwise limited the review of hospital records to convenient sampling sizes.[3,8] Obvious differences include the concurrent, not retrospective, nature of our review, the routine review in our institution of all admissions and every patient day (no sampling), and the serious conditions of our patients—about 75% of admissions are through the emergency department or urgent from the outpatient clinics. In our institution only about half the total hospital days detected as inappropriate by the screening criteria are confirmed after physician review and receiving additional information from the responsible physician. Even so, the days detected by screening (and no further review) amount to only 2% to 3% of total hospital days. The acute nature of the need for hospital admission of our patient population, therefore, is likely an important factor in explaining the much lower rates of inappropriate hospital utilization detected at this institution.

Further, our data reflect practices for admitting patients to hospital since 1985, whereas much of the reported data were derived from earlier times, perhaps reflecting "softer" requirements—for example, annual admission rates declined more than 20% from 1975 to 1985. Consequently, reasons for the discrepancy between our data and those in the literature are probably multiple: severity of illness and patient mix, sampling errors, changes in physicians' practices regarding admissions, the use of ambulatory surgery facilities, and the knowledge of our physicians that all admissions and each day of hospital stay will be reviewed. Our attempts to customize the screening criteria for the appropriateness of admission or continued stay have probably had only minor effects in decreasing the number of cases detected and denied.

Effective utilization review is useful in providing quantitative information to hospital management regarding the consequences of scheduling problems, equipment failures, the lack of a lower level of care facilities in the community, and, potentially, the inappropriate use of intensive care and ancillary services. In addition, data are obtained routinely indicating which services or physicians are having the greatest difficulty in the efficient diagnosis, treatment, and discharge of patients. With the utilization review data, it becomes easier to appeal adverse reimbursement decisions and to do so in a timely fashion. Justifications for extending hospital stays and for special treatments are more readily available.

At UCDMC utilization review is coupled tightly with discharge planning, both activities occurring in the same location under the same direction. This arrangement permits an earlier assignment of priorities to arranging out-of-hospital patient care when needed and facilitates efficient discharges.

Quality of care may be aided by the kind of review done in utilization review and by the data obtained. Specific examples would include analyzing premature discharges, early or inappropriate readmissions, daily documenting in the medical record a patient's progress, and any problems in terms of diagnostic procedures or responses to therapy. As mentioned, delays in obtaining the needed diagnostic or therapeutic services can be identified routinely. Resource use, appropriate and inappropriate, can be monitored for each of the hospital services and even for each physician.

Still, there are problems in the utilization review process as applied at our institution. Thus far the process has not been extended formally to include the appropriateness of stay in special care units, such as intensive care. This analysis would have obvious value in cost containment and potential quality control and is a likely area for expanding our review. We have not applied the process described here to the use of ancillary services, but this also may have merit. It should be recognized also that because the review operation takes place on a Monday-through-Friday basis, there may be a delayed recognition of inappropriate admissions and continued hospital stays, but subsequent review should still identify these.

A notable difficulty exists in the suitability of the screening criteria. For many services with highly specialized diagnostic or therapeutic programs and patients with complex and severe illnesses, the criteria are frequently inadequate. We have attempted to address this by customizing the criteria for each clinical service; the results have been positive but modestly so. Other difficulties arise from inadequate or inappropriate documentation in the medical record. Frequently what is written is the current status of a patient as opposed to progress and plans or any explicit analysis of the reason(s) for that patient being in the hospital. Because the available information may not meet the criteria, these patient-days are referred to the physician reviewer, and it becomes necessary to obtain additional information from the patient's physician. This process is frustrating and wastes

physicians' time, even when successful. Because the reviewer cannot always reach the responsible physician, a decision is sometimes made with less than full information. Clearly in these circumstances the error rate will be increased. We have attempted to address some of these problems by giving presentations to the major departments explaining the process and indicating where the departments and individual physicians can be most helpful to us and to the hospital and, potentially, to their own patients. While cooperation has been variable, most physicians have responded satisfactorily to utilization review activities.

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Acetaminophen Toxicity in Alcoholics

WHY DO ALCOHOLICS tend to develop acetaminophen toxicity? Well, they have a tendency to take larger than normal doses over a 24 to 48 hour period because they are careless and confused—a tendency to take repetitive doses. But there also is increased susceptibility to a standard dose. Alcohol enhances the activity of the cytochrome P-450 system—it induces it. The alcohol decreases synthesis of glutathione, in addition to which the alcoholic's life-style leads to depleted glutathione. Third, it is probable that alcohol enhances membrane vulnerability.

—HYMAN J. ZIMMERMAN, MD

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Lessons From the Practice

Doctors, Patients, and Fear

ALEXANDRA M. LEVINE, MD, *Los Angeles*

It is my experience that if there is one common denominator among all of our patients, that commonality is most certainly fear: fear of the illness, fear of the unknown, fear of the loss of control over one's own life, and—I hate to admit it—fear, as well, of the physician. The physician has come to symbolize the figure of knowledge, of authority, of control. It takes a strong patient to stand up and demand to know, or question what we have said, or question what we have not said. And, oftentimes when the patient is strong enough to question us, we take offense and consider the patient difficult. Patients are afraid, and our actions do not encourage them to ask those questions that might alleviate their fear. They do not want to offend us. Let me illustrate.

Several years ago, a patient was referred to me, a middle-aged man who had been diagnosed as having malignant lymphoma. He was a dean of a nearby college, with a PhD in psychology, so we may assume that he was well-educated and quite psychologically aware. When he was told that he had a malignancy, he had difficulty in coping. He refused to believe that he had lymphoma, and he refused the chemotherapy that was offered. He went to many doctors, seeking someone, I am sure, who would tell him that he did not have lymphoma at all. In this setting, he eventually found a "doctor" who was, in fact, a fraud, a "cancer quack" who is currently in jail for this crime. In any event, this person said to the patient that he had a treatment that was guaranteed to cure him forever if he took it; without such treatment, he guaranteed that the patient would be dead in two months. The "quack" wanted $60,000 cash to begin, and the patient, even though he was extremely well-educated, was frightened to the extent that he did not understand and could not see how absurd these claims really were. The patient put a lien on his house to get the required money, and at that point his wife sought help from the Cancer Information Service. It is from this service that the patient was referred to me.

When the patient first entered my office, he was extremely ill at ease—sweating, pacing, and so forth. He had a large lymph node mass that was visible and that seemed to be pressing on his trachea so that it was somewhat difficult for him to speak. I began by educating. I explained what lymphoma is, what chemotherapy is, what side effects are, what were the expectations of this treatment, and so on. I wrote everything down, as I usually do. We went over all the patient's questions and the answers to those questions, and, at the conclusion of several hours, the patient said to me that he had been convinced and that he wanted to go ahead and get started with the chemotherapy treatment right then. I could not do it, simply because I did not have all the tests and radiographs that were required. An arrangement was made that we would obtain the needed tests, and the patient would come back to me in two days' time. In the meantime, I examined him and carefully wrote down all of the disease parameters—all of the lumps and bumps—recording the dimensions of these various lesions so that I could follow them in time to ascertain the effectiveness of the therapy. The large lymph node in his neck, for example, measured about 9 cm in diameter, while his spleen was 12 cm below the left costal margin.

When the patient returned 48 hours later, he looked better. He was not sweating or pacing anymore; he looked more relaxed and comfortable. The first thing he said to me was that I should measure the lumps because he thought they had gotten smaller. I was intrigued and extremely impressed with what I found: the cervical tumor mass that had measured 9 cm only two days before was now 5 cm, and the spleen, which had been 12 cm from the costal margin, was now 9 cm. In other words, both masses had become significantly smaller during that two-day period. I said to him, "Darn, if only I had started the chemotherapy on Wednesday, I could have proved to you that it works." He replied that I had started the treatment on Wednesday—and the treatment was education and peace of mind. Apparently, when his mind was at ease, as opposed to stressed and frightened, some chemical or immunologic event must have occurred, which apparently has a positive effect on malignant lymphoma.

What did this patient teach me? Many things, obviously. First, though, he taught me that all patients are afraid, whether or not they are educated, whether or not they are actually aware of that fear and able to voice it. I also learned that a patient who is afraid is very likely to do poorly when compared with a patient who is comfortable and at peace with the situation at hand. This patient taught me something else, though. He taught me how valuable the time spent in education can be. To educate the patient is to begin to alleviate the underlying fear. After all, in the final analysis, we are all afraid of the unknown.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

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1. Data on file, Lilly Research Laboratories.

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AXID®

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Brief Summary

Consult the package literature for complete information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General* — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests — False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions — No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

PV 2096 AMP [013089]

Additional information available to the profession on request.

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July 31-August 3—**Practical Orthopaedic Sports Medicine.** Children's Hospital Oakland at Hyatt Regency, Waikoloa, Kona Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Stuart Zeman, MD, 2999 Regent St, No 203, Berkeley 94705. (415) 540-8686.

August 2-6—**Wilderness Medicine: '89.** American College of Emergency Physicians California Chapter at Squaw Valley, Lake Tahoe. Wed.-Sun. 22 hrs. $395. Contact: Jackie Silva, MD, PO Box 321, Yreka 96097. (916) 842-4667.

August 11-12—**Office Practice Enhancement: Non-invasive Diagnostic Testing.** Medical Education Collaborative at Lake Tahoe, Nevada. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

August 25-27—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 19 hrs. $235. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

September 8-9—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Napa. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 13-15—**Primary Care Medicine: Principles and Practice.** UCSF at The Portman, San Francisco. Wed-Fri. 20 hrs. $385. Contact: UCSF.

September 23—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Scripps Amphitheater. Sat. 6 hrs. $50. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

October 14—**29th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott Hotel. Sat. Contact: Sylvie Tarro, (213) 641-8152.

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 3—**Alzheimers Update.** UCD at Sacramento. Fri. Contact: UCD.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

November 30-December 3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Las Vegas. Thurs-Sat. 18 hrs. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

IDAHO

July 27-29—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701.

August 7-8—**Northwest Regional Perinatal Conference—Current Issues in OB/GYN, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Mon-Tues. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 15-16—**9th Annual University of New Mexico/American College of Emergency Physicians Emergency Medicine Symposium.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

June 23-24—**Certification Update for Radiographers.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

July 17-20—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Ruidoso. Contact: Anne Woodrow, NM Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 20-22—**General Surgical Postgraduate Course.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 7-9—**Concepts and Controversies in Perinatal Care.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 9-10—**First American Cancer Society Interdisciplinary Cancer Conference.** Bishop's Lodge, Santa Fe. Contact: Stephanie Gooch, American Cancer Society, NM Chapter, 5800 Lomas NE, Albuquerque 87110. (505) 262-2336.

September 15-16—**Essentials of Health Care for the Elderly.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 15-16—**New Mexico Chapter, American College of Surgeons—Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: NM Chapter, ACS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

September 22-23—**Southwestern Psychiatric Symposium on Schizophrenia and Depression.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

October 12-14—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah.

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CONTINUING MEDICAL EDUCATION

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Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 18-23—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 12-14—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Salt Lake City. Contact: Barbara Saffel, (801) 466-3500.

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon. Jackson Hole, Wyoming. Contact: Midge Beckman, (801) 581-7480.

July 20—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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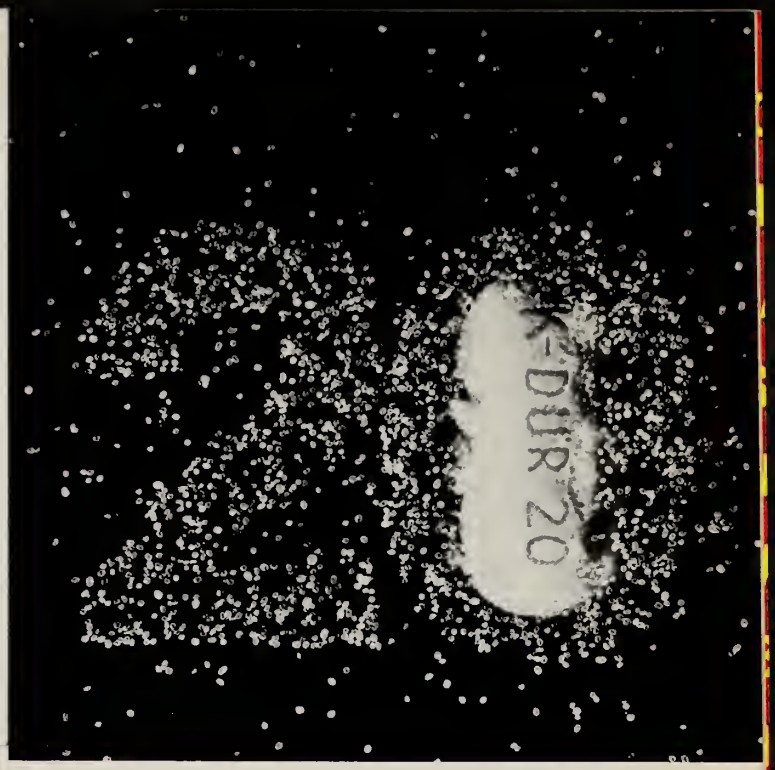

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Please see next page for brief summary of prescribing information.

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K-DUR™ Microburst Release System®
(potassium chloride) Sustained Release Tablets

INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40-50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE).** There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS);** other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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World leader in drug delivery systems.

CONTINUING MEDICAL EDUCATION

(Continued from Page 735)

September 28-29—**Laser Surgery: General Surgery ND: YAG, CO** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

October 12-13—**Laser Surgery: Gastroenterology ND: YAG** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 16-18—**Pediatrics Update.** Oregon. Fri-Sun. Contact: U/W.

June 26-27—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: (206) 627-7137.

June 28-30—**Comparative Implants for Orthopaedics.** Seattle. Wed-Fri. Contact: U/W.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349.

August 7-12—**Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 12—**Instrumented Measurement of A/P Knee Laxity.** Seattle. Sat. Contact: VMMC.

September 11-15—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 15-16—**Urology Update.** Seattle. Fri-Sat. Contact: VMMC.

October 6—**23rd Annual Cancer Conference: Innovative Management of Cancer Patients.** Seattle. Fri. Contact: VMMC.

October 27-28—**Acid-Peptic Disease: New Perspectives.** Seattle. Fri-Sat. Contact: VMMC.

November 3—**The Injured Knee: Diagnosis, Treatment, and Therapy.** Seattle. Fri. Contact: VMMC.

November 10—**Outpatient Treatment of Infections: Oral Antibiotic Therapy.** Seattle. Fri. Contact: VMMC.

December 1—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Contact: Midge Beckman, (801) 581-7480.

October 6—**Update on Infectious Diseases.** West Park Hospital, Cody. Contact: Elaine Nestell, Education Director, West Park Hospital, 707 Sheridan Ave, Cody, WY 82414. (307) 527-7501, ext 250. ◆

SPECIAL ISSUES

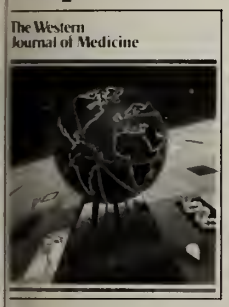
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

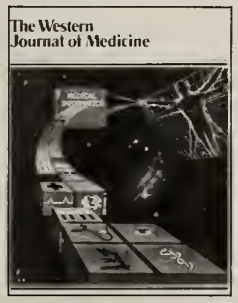
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



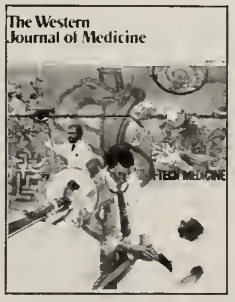
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



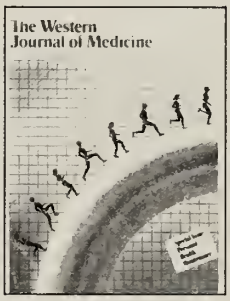
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



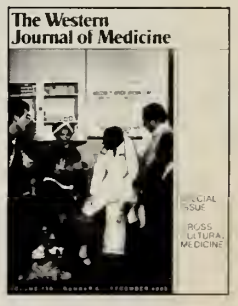
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall 1988. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

OB/GYN, NORTHERN CALIFORNIA. Position available for BE/BC OB/GYN in 10 person department with new LDR suite, family centered Obstetric practice as well as full Gynecology practice. 20 miles south of San Francisco, adjacent to large wooded areas, and easy access to ocean. Prepaid medical group with competitive salary and very generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EEO/AA.

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Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Pediatrics, General Surgery (breast disease focus), OB/GYN. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

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BC/BE GENERAL INTERNISTS needed for multispecialty group in Sacramento, California. We are an established Department of Medicine with close university affiliation. Pleasant practice setting where physicians are free to practice the highest quality medicine with full access to diagnostic, therapeutic, and consultative services. Our patients are from a growing Sacramento community with a good cost of living. Our hospital provides a substantial part of University of California Davis residency training program. Excellent in-house continuing medical education program. We are a successful, stable medical group experiencing robust growth. Outstanding starting salary and advancement. Full benefits and retirement. This is a quality career opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, 2025 Morse Ave, Sacramento, CA 95825.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

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BC/BE FAMILY PRACTITIONER for nonprofit community clinic in redwood country. Prefer OB/Pediatrics training, but OB negotiable. C-sections optional. Quality care for underserved and more affluent in rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

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FACULTY POSITIONS. The San Jose Medical Center Family Practice Residency Program has an opening for full-time and part-time faculty. Positions include direct patient care (including OB), resident teaching and administrative duties. Program affiliated with Stanford University School of Medicine. Competitive salary and benefit package. Please direct inquiries to Robert Norman, MD, Director, 25 N. 14th St, Ste 1020, San Jose, CA 95112; (408) 977-4507.

FAMILY PRACTITIONERS AND INTERNISTS needed part-time for staffing ambulatory care clinic. Our clinic operates seven days a week during days and evenings and provides episodic care on a same-day basis. Our patients are from a growing Sacramento community with good cost of living. Physicians may choose to work one to 10 half-days or evenings per week with wide flexibility. Full benefits and retirement if working six or more half-days a week on a steady basis. We are a successful, stable medical group experiencing robust growth. Please call John Petitt, MD, (916) 973-5560 or send CV to John Petitt, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825.

WASHINGTON. Openings for career oriented Emergency Physicians, BE/BC in Emergency or Primary Medical specialty. In a Seattle metropolitan hospital with 48,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Shelly Tulloch, 8041 S. 180th, Ste 100, Kent, WA 98032; (206) 575-2595.

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ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Norman Olson, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

(Continued on Page 740)

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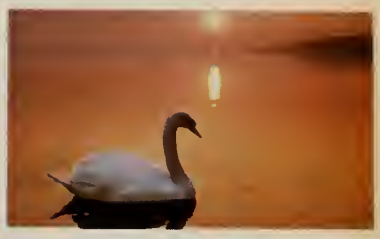

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For Brief Summary, please see following page.

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986;80(3B) 17-21 2. Luckin I, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987;23 207-211 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987;82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride.
Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment
Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.
Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures
Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).
Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.
Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid
Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.
Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed
Nursing Mothers—Administration to nursing women should be avoided if clinically possible.
Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.
Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.
Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.
Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.
Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary
Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%
Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.
Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.
Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.
Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).
Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress No deaths have been reported in humans either with deliberate or accidental overdosage.
Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.
For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.
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GENERAL INTERNIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Norman Olson, Chief of Medicine, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

FAMILY PRACTICE, PUGET SOUND. 27 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to John Houser, Executive Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

PULMONOLOGIST, BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Norman Olson, MD, Chief of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063. EOE/AA.

CARDIOLOGIST, invasive/noninvasive, to take over northern California practice, revenues approximately $600,000. Also separate ultrasound testing business (with client base), and equipment for sale. Call Bradshaw Associates, (415) 376-0762, 21 Altamount, Orinda, CA 94563.

GENERAL INTERNIST, with or without subspecialty training, being sought to join busy seven member Internal Medicine practice in downtown Sacramento. One to two years of guaranteed salary to start. Contact Joshua Hoffman, MD, at (916) 733-5097, or send CV to 2801 K St, #520, Sacramento, CA 95816.

NORTHERN CALIFORNIA. The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. University associated residency program. Competitive salary and comprehensive benefits package. 90 miles from San Francisco and Sierra skiing. California license required. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678.

WASHINGTON. BC/BE Family Physician for a clinic-based immediate care center. The clinic is a 32 physician multispecialty group. Guaranteed income with excellent benefit package. Ideal opportunity for active practitioner who wants to slow down. Send CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

UROLOGIST, southern California. Urology group seeking new highly qualified BC partner. Ability in all radical surgery, ESWL, Endourology, prostheses, etc desired. Excellent smog-free coastal locale. Busy, expandable practice. Send CV to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

(Continued on Page 741)

(Continued from Page 740)

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Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

INTERNAL MEDICINE. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an Internist for full-time work. Competitive salary. Excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

FAMILY PRACTITIONER. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks a Family Practitioner for full-time work. Competitive salary. Excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

SAN FRANCISCO BAY AREA. Large multispecialty, multi-facility group practice is seeking a BC/BE physician to join their expanding Occupational Medicine Department. Range of practice includes pre-employment physicals, diagnostic evaluations; treatment of on-the-job injuries. Competitive salary, excellent benefits and incentive plan, paid malpractice. Located in the South Bay which offers many cultural facilities, recreational activities, fine dining, outstanding scenery and climate, and easy access to San Francisco, Monterey, and the Sierra Nevada. For further information, please send CV or contact Maureen Forrester, Physician Recruitment, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

NEUROLOGIST
for Full-Time Position in San Francisco Bay Area

Nation's largest HMO Kaiser Permanente seeks BE/BC Neurologist for immediate opening. EEG experience necessary; EMG a plus. Resident teaching opportunities. Academic affiliations encouraged. Competitive compensation and outstanding benefits including paid vacation, continuing education, life/medical/dental insurance, professional liability, retirement plans, and full shareholdership within three years with profit-sharing. Send CV to:

Joel Richmon, MD
Dept of Neurology
Kaiser Permanente Medical Center
280 W. MacArthur Blvd
Oakland, CA 94611
Phone: (415) 596-6511

PHYSICIANS WANTED

PACIFIC NORTHWEST
GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

Allergy	OB/GYN
Cardiology	Orthopaedics
Dermatology	Otolaryngology
Family Practice	Urgent Care
General and Vascular Surgery	Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

SAN FRANCISCO. Temporary full- and part-time positions available beginning June 15 for physicians BC/BE in Emergency Medicine, Internal Medicine, or Family Practice. Admitting Physician to provide inpatient care only; 24 hour shifts; acute care hospital in San Francisco; no call required; paid malpractice. Send CV to Chase Dennis Group, 400 Taylor Blvd, Ste 330, Pleasant Hill, CA 94523; (415) 676-2555.

INTERNAL MEDICINE, NORTHERN CALIFORNIA. You have a unique opportunity to join the area's leading multispecialty private medical practice. A position is available immediately for a BE/BC Internist. All subspecialties welcome to apply. Generous salary, bonus provision, fringe benefit package, and early membership in the corporation. Accept the challenge; become part of our competitive, growing organization. Experience the good life—wonderful restaurants, beautiful scenery, great weather, cultural facilities, easy access to beaches and mountains. Send CV and receive further information by contacting Christy Jensen or Maureen Forrester, Physician Recruitment, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833, (408) 282-7757.

MEDICAL ONCOLOGIST BC/BE to join expanding 32 physician multispecialty group practice located in the foothills of the Blue Mountains in the state of Washington. The clinic serves a population area of 150,000. Full range of Radiation Oncology services are available in the community. Excellent schools, cultural and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE. Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

INTERNIST seeks BC/BE partner for historic rural area. Bustling practice with limitless opportunity serving Washington state island community. Safe and scenic. Convenient tertiary centers for referral and CME. Full service local hospital. Send résumé to PO Box 840, Coupeville, WA 98239.

INSTITUTION PHYSICIAN NEEDED to staff the Wyoming State Training School in Lander, Wyoming. We have 360 clients in an institutional setting for acute care in an 18 bed health care center. There is a staff of three physicians and one Physician's Assistant for total medical services. Salary commences at $55,326 per year. Attractive benefits, no overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Hwy 789, Lander, WY 82520; (307) 332-5302. An Equal Opportunity Employer.

Medical Director
In the Heart of San Bernardino County

Young, rapidly expanding 13-physician multi-specialty group seeks experienced medical director. Must be a leader with excellent interpersonal skills, high standards, strong HMO/UR background, and BC in primary care specialty. Clinical-60%; administrative-40%. Strong administrative team; excellent compensation package. New hospital. Outstanding community choices.

Leon Pettijohn, VP
Pacific Physician Services
(714) 887-1444

(Continued on Page 742)

(Continued from Page 741)

PHYSICIANS WANTED

WANTED
General Surgeon, BC/BE, to join BC Surgeon in challenging North Coast California Redwood Country practice. Attractive compensation package with income guarantee, malpractice and health insurance coverage, and partnership participation. Area is one of great scenic beauty and desirability for individual who enjoys outdoor living, hunting, and fishing **Contact M. Mullem, MD, FACS, at (707) 464-7436, or send CV to 418 9th St, Crescent City, CA 95531.**

CALIFORNIA. Outstanding practice opportunities for medical directors, primary care and specialist physicians too numerous to mention in disciplines of OB/GYN, Allergy, Family Practice, Pediatrics, Pulmonary Disease, Invasive and Noninvasive Cardiology, Otolaryngology, Gastroenterology, Neurology, Orthopaedic Surgery, Neurosurgery, and Urology. As retained consultants to more than 25 hospitals, group practices, and HMOs in northern and southern California, we can discuss each practice in detail. Please call or send a CV for additional information. Complete confidentiality assured. Contact Ken Baker at (415) 981-7424 (collect). Physician Search Group, 50 California St, Ste 400, San Francisco, CA 94111.

SAN FRANCISCO BAY AREA. Excellent opportunity to join three Internists in established group practice. Prefer Primary Internist or Internal Medicine subspecialist. Attractive, well equipped facilities adjacent to 380-bed JCAH hospital. Send CV or contact George Gordon, MD, 2101 Forest Ave, #220, San Jose, CA 95128; (408) 275-1727.

OB/GYN—OPPORTUNITIES. Three private practices: East Bay (two), North Bay. Also recruiting for group practice: BC/BE physicians in northern California and nationwide. Excellent salary/benefits. Send CV or call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

WASHINGTON. General Internist BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is composed of 32 physician multispecialty group. Guaranteed income, plus excellent benefits. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

BC PHYSICIANS MANAGED CARE

Cost Care, the nation's leading health care cost management company, is seeking full- or part-time BC physicians to staff the Medical and Mental Health Services departments. Ideal candidates will have:

- Three to five years clinical experience in a managed care setting
- Utilization Review expertise
- Strong interpersonal skills

Send résumé/CV to:

Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

PHYSICIANS WANTED

IMMEDIATE OPENINGS IN CALIFORNIA CENTRAL COAST GROUP PRACTICE

Growing multi-specialty group practice in Ventura, California seeks:

BC/BE
- Orthopedic Surgeon
- Pediatrician
- Family Practitioners
- Cardiologist
- Pulmonologist
- Psychiatrist
- Internist

We offer competitive compensation and excellent benefits; shareholdership option after 1 year. Located 60 miles north of Los Angeles, our community is one of the most beautiful areas in California, with excellent schools, a strong economy, and a wide range of cultural and recreational activities. Call for more information. Send inquiries and Curriculum Vitae to:

A Tradition of Service Since 1950

Buenaventura Medical Clinic

2705 Loma Vista Road Ventura, California 93003 (805) 648-2571

INFECTIOUS DISEASE. Dynamic hospital based Internal Medicine/Pulmonary four man group seeks BE/BC Infectious Disease associate. Some critical care skills required. Beautiful waterfront community near Seattle. Outstanding financial package. Send CV to Number 155, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS — FULL-TIME TRAVEL REQUIRED (one year minimum). Westat, a health research organization, is seeking physicians for the third National Health and Nutrition Examination Survey sponsored by the U.S. Public Health Service. Individuals will be part of a highly trained medical team conducting physical examinations in mobile exam centers traveling to 88 U.S. cities through 1993. Physicians must be licensed in one state and be BC/BE in Internal or Family Medicine. Competitive salaries, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248 or (301) 251-8248 or send CV to Westat, Inc, 1650 Research Blvd, Rockville, MD 20850, Attn: B. Geline. EOE/M/F/V/H.

FAMILY PRACTICE BC/BE position available in a satellite clinic of a large Seattle area multispecialty group practice. Diverse patient population including managed care, retired military, and fee-for-service. Attractive salary and benefits. Contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S, Seattle, WA 98144; (206) 326-4111.

FAMILY PRACTICE. Private practices located in San Francisco, Alameda County, Sacramento, Modesto-Stockton. Recruitment opportunities in other areas of California and nationwide. Send CV or call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

BOISE, IDAHO. BC/BE Internist or Family Practice. Idaho Department of Corrections needs full-time staff physician; also will assume Medical Director role. Chief duties are clinical. Must be able to achieve hospital privileges. Minimal call; excellent area for all outdoor recreation. Good place to raise family. Salary $80 to $92K first year based on qualifications. No overhead. CV to Steve Stedtfeld or Dr Kelly Mutch, IDOC Medical Services, Box 14, Boise, ID 83707; (208) 334-2318 or (208) 336-0740.

CALIFORNIA—FRESNO, FAMILY PRACTICE. Family Practice, Emergency Room, Occupational Medicine Physician BE/BC to join expanding group to provide Family Medicine, Occupational Medicine and Urgent Care Medicine in a well equipped clinic setting. Competitive salary with incentive plan, paid malpractice. Send CV to Medical Director, 3636 N. First St, Ste 162, Fresno, CA 93726; (209) 221-2022.

WANTED BC/BE PEDIATRICIANS

Nighttime pediatrics clinic. For information see article in *Contemporary Peds*, July 1987. Part-/full-time 20 to 40 hours per week. Salary negotiable. Inquire c/o

Jed Dunford
279 East 5900 South
Murray, UT 84107

(Continued on Page 744)

Millions of Americans are being asked to look out below

The GSE™: What it means to you

Across the country, sexually active adults will soon be encouraged to do a special health check called a GSE... a genital self-examination. A simple examination to check for potential signs of a sexually transmitted disease (STD).

The GSE is the heart of a nationwide campaign to heighten public awareness of STDs. This program is sponsored by Burroughs Wellcome Co. in conjunction with major medical associations.*

Sexually active adults will be urged to send for a free guide that explains how to perform a GSE. The guide discourages self-diagnosis and encourages seeing a physician if anything suspect is found.

As the GSE campaign gains momentum, you may be seeing more patients coming to your office with concerns about sexually transmitted diseases. While STDs are currently regaining their foothold on the American population, the GSE program offers a promising outlook for reducing their spread.

*The American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, and the American Osteopathic Association.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

Burroughs Wellcome Co.,
Research Triangle Park,
North Carolina 27709

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April 1989 ZO-970

(Continued from Page 742)

PHYSICIANS WANTED

PHYSICIANS
Ambulatory Care Clinic
CALIFORNIA

JSA, Inc., an internationally recognized healthcare management and consulting organization, is offering physicians full and part-time positions in a challenging and busy Family Practice Primary Care Clinic located in San Diego, CA.

The following generous benefit package is offered to Physicians:

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Paid malpractice insurance**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

Qualifications include Board Certification in Family Practice, Pediatrics or a Primary Care Specialty, current state licensure and ACLS BCLS.

For additional information, please contact: Susan Bray, Recruiting Director, JSA, Inc., Box 1305, Columbia, MD 21044. (301) 964-2811.

JSA, Inc.

An Equal Opportunity Employer

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful ambulatory health care network. Generous guarantee, incentive plan and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE primary care specialists preferred. Contact Bob Morris, MD, FACEP, 223 Mt. Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

FAMILY PRACTICE. California BC/BE Family Practice Physician sought by large medical group for a rural satellite location 15 miles from Sacramento. Competitive salary and benefits first year. For more information, please send current CV to Warren J. Boyer, Jr, MD, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

NAPA, CALIFORNIA. BC Internist. Location in Napa, heart of the wine country. Close to San Francisco. Offering start-up in personal private practice. Send CV and two letters of recommendation (Department Chief if applicable) to Alvin L. Block, MD, 3230 Beard Rd, Napa, CA 94558; (707) 257-1550.

LOS ANGELES COUNTY—OB/GYN. A busy and successful two physician group, practicing in a Los Angeles County community of 115,000 for the past five years, is now seeking another member. For more information, send your CV to Manager, Professional Relations, Humana Inc, Dept HH-6A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

DERMATOLOGY. Two opportunities in northern California. One private practice for sale and one placement as associate. Send CV or call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

ROSEVILLE. Immediate opening for BC/BE Family Practitioner. Ours is a satellite clinic in a group model HMO. Practice is primarily adult care with no OB or night call. Attractive salary, comprehensive benefit package, opportunity for shareholder status available. Malpractice provided. Contact Richard Fury, MD, The Permanente Medical Group, Inc, 1001 Riverside Ave, Roseville, CA 95678; (916) 784-4620.

GERIATRICIAN—PHOENIX. A regionally recognized, multispecialty group here is now seeking a Geriatrician to provide ongoing support for their many patients. Send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-6C, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

CARDIOLOGIST—ARIZONA. A regionally recognized 15 physician Cardiology group in Phoenix is now seeking to add one Noninvasive and two Invasive Cardiologists. Their new offices are located adjacent to our 314-bed hospital there. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-6B, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

OCCUPATIONAL MEDICINE. Full- or part-time physician needed to do pre-employment and environmental examinations. Position requires ability to make work-fitness assessments. Direct patient care also possible. Salary $78,000-85,000, pension plan, and malpractice insurance. Call or send CV to Robert Goldberg, MD, City of Los Angeles, Personnel Dept, 1401 W. 6th St, Los Angeles, CA 90017; (213) 485-4641.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural lifestyles. Contact Dr Donn Cobb, Health Officer, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

PHYSICIANS WANTED

INTERNISTS

Practice in beautiful

Northern California

Hospital-based internists immediately needed at prestigious 132-bed Redding Medical Center. Large open-heart surgery program. Practice limited to inpatient general med. Xlent benefits (CME, vacation), min. guarantee of $125,000 annual take-home pay, plus FFS incentives, paid malpractice, and hospital provides billing. Flexible rotating call schedule. Incredible opportunity!

Hospital lies in the shadow of Mt. Shasta. Great recreational and family area. Contact:

Gary L. Groves, MD
(714) 825-4401 in CA
or (800) 338-4798

SAN FRANCISCO PENINSULA (SAN MATEO). Two Internists seeking associate for General Internal Medicine practice in San Mateo on San Francisco peninsula. A 250-bed hospital one block from the office. Weekly continuing medical education program in the hospital by Stanford professors. Ideal weather. Mountains and ocean nearby. Excellent call rotation. 18 miles from Stanford and University of California medical schools. Send résumé to Stephen Marks, MD, 109 St. Matthews Ave, San Mateo, CA 94401; (415) 343-2737.

UNIVERSITY PHYSICIANS. Student Health Service, University of Wyoming, Laramie, is seeking two physicians for full-time employment. Applicants must have a Medical Doctor's degree plus be BC/BE by either AAFP or American Board of Internal Medicine. Must have a license or qualify for licensure to practice medicine in the state of Wyoming. Prefer candidate to have at least four years of primary care experience. Physicians to join two full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy. Salary commensurate with qualifications and experience. Closing date: July 5, 1989, and continued until position is filled. Applications may be obtained from Personnel Office, University of Wyoming, Box 3422, Room 139 Wyo Hall, Laramie, WY 82071. The University of Wyoming is an EO/AA employer.

GENERAL SURGEON. Established young, mellow but compulsive General Surgeon in southern California seeks an associate so he can spend more time with his young children. If interested send CV and personal description to Number 159, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 749)

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AIR FORCE MEDICINE

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Air Force medicine is one of our best benefits. The Air Force needs physicians such as you to keep it that way.

Most administrative responsibilities are in the hands of others, giving you the time to give full attention to the patients' needs. Our hospitals are staffed with dedicated, competent professionals to assist you.

You'll have time for your family and to keep abreast of the latest methods and technologies that you don't have time for now. We also offer unlimited professional development and financial security.

Find out more about Air Force medicine. Contact your nearest Air Force recruiter. Call

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AIR FORCE

The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

WHEN ACID REFLUX ERUPTS

Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source—an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® Tablets

ranitidine HCl/Glaxo

150 mg tablets bid

1. Sontag S, Robinson M, McCallum RW, et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. *Arch Intern Med* 1987;147:1485-1491

Please see next page for Brief Summary of Prescribing Information

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer, hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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(Continued from Page 744)

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Exciting opportunity for Dermatologist to develop an interesting and challenging practice in sophisticated metropolitan Los Angeles area. Easy access to major academic centers, cultural and recreational activities. Superb salary and benefits. Send CV to:

Director/Professional Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203
or call collect (818) 500-6236

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

EMERGENCY PHYSICIAN. Los Angeles area. Active base station, community hospital, fee-for-service. Malpractice, etc. Dynamite opportunity. Call for details. Dr Murchison, (714) 627-6111, ext 300.

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 14-17, 1989, Westin Hotel, Vail.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-29, 1989, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1990, date and location to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1990, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 13-15, 1989, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 28-October 1, 1989, SEATAC Red Lion, Seattle.

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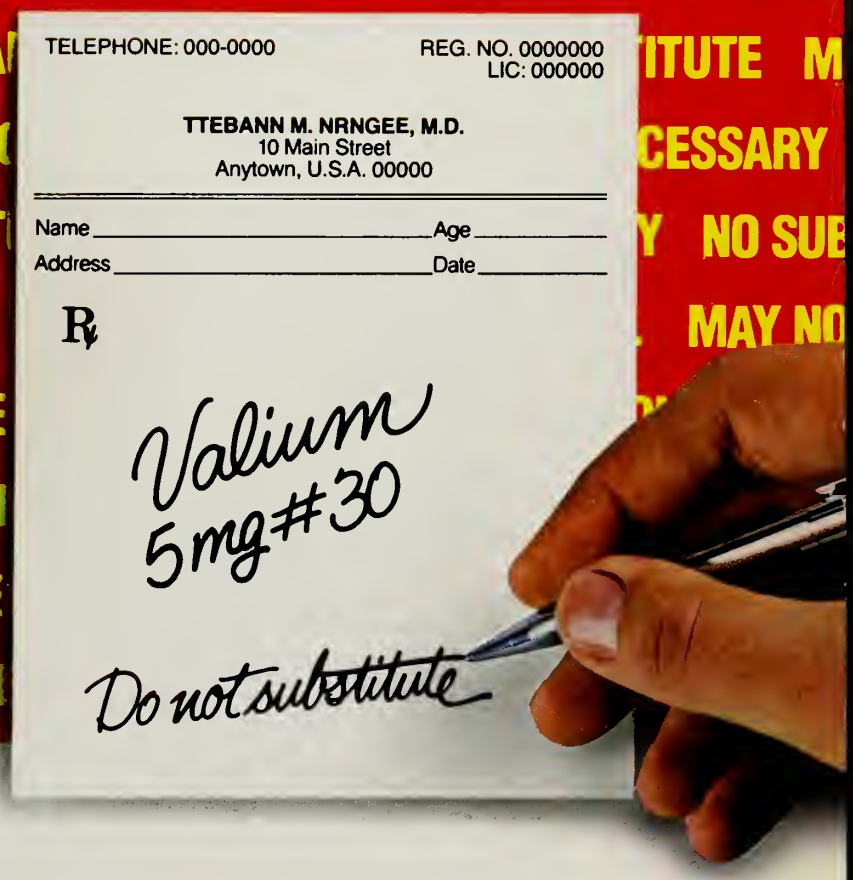

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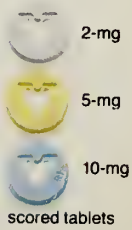

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